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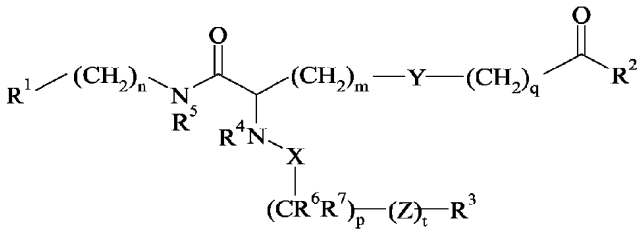

(I)

(57) Abstract: The present invention relates to compounds of formula I: or pharmaceutically acceptable salts or stereoisomers thereof. The compounds of the present invention are inhibitors of histone deacetylase (HDAC) and are useful for treating cellular proliferative diseases, including cancer. Further, the compounds of the present invention are useful for treating neurodegenerative diseases, schizophrenia and stroke among other diseases.

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AMINO ACID DERIVATIVES AS HISTONE DEACETYLASE (HDAC) INHIBITORS

The present invention relates to amino acid derivatives that are inhibitors of histone deacetylase (HDAC). The compounds of the present invention are useful for treating cellular proliferative diseases, including cancer. Further, the compounds of the present invention are useful for treating neurodegenerative diseases, schizophrenia and stroke among other diseases.

In eukaryotic cells the orderly packaging of DNA in the nucleus plays an important role in the regulation of gene transcription. Nuclear DNA is ordered in a compact complex called chromatin. The core of the complex is an octamer of highly conserved basic proteins called histones. Two each of histones H2A, H2B, H3 and H4 associate and DNA winds around the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. One molecule of histone H1 is associated with each wound core which accommodates approximately 146 bp of DNA. The cores are, in turn, packaged into a compact regular structure with about 200 bp of DNA between each core.

The amino-terminal tails of the histones are subject to post-translational modification, in particular by acetylation of lysine. Histone deacetylases (HDACs) and histone acetyl transferases (HATs) determine the pattern of histone acetylation, which together with other dynamic sequential post-translational modifications might represent a 'code' that can be recognised by non-histone proteins forming complexes involved in the regulation of gene expression. This and the ability of histone deacetylases (HDACs) to also modify non-histonic substrates and participate in multi-protein complexes contributes to the regulation of gene transcription, cell cycle progression and differentiation, genome stability and stress responses.

Eleven members of the HDAC family have been identified in humans, which share a conserved catalytic domain and are grouped into two classes: class I (1, 2, 3, 8), homologous to yeast Rpd3; class IIa (4, 5, 7, 9) and IIb (6, 10), homologous to yeast Hdal. HDAC11 shares homologies with both classes, but is at the same time distinct from all the other ten subtypes. Interest in these enzymes is growing because HDAC inhibitors (HDACi) are promising therapeutic agents against cancer and other diseases. The first generation of HDACi were discovered from cell-based functional assays and only later identified as HDAC class I/II inhibitors. Present HDAC inhibitors are pan-specific or poorly selective. Those that entered clinical trials all show similar adverse effects, mainly fatigue, anorexia, hematologic and GI-toxicity, that becomes dose-limiting in clinical trials. It is not at all clear whether the antitumor properties of HDAC inhibitors are due to their lack of specificity or are the consequence of hitting one or few "crucial" subtypes. This question is of considerable interest because it may open the way for the development of novel, more sensitive compounds with possibly enhanced efficacy and/or tolerability. More recent studies were therefore directed to better define the biological function of different class members and to devise subtype-selective enzymatic assays to assist in the development of improved cancer chemotherapies.

The class IIa HDACs contain a highly conserved C-terminal catalytic domain (~ 420 amino acids) homologous to yHDA1 and an N-terminal domain with no similarity to other proteins. The activity

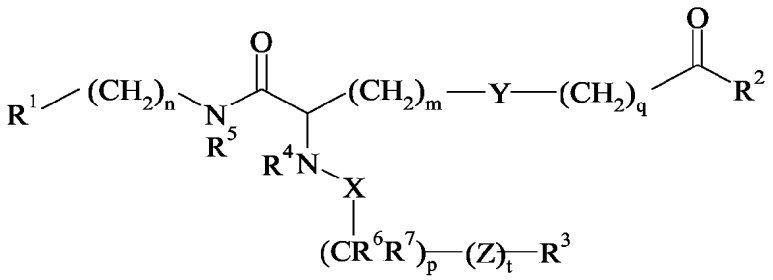
of the class IIa HDACs is regulated at several levels, including tissue-specific gene expression, recruitment of distinct cofactors and nucleocytoplasmic shuttling. Whereas most class I HDACs are ubiquitously expressed, class IIa HDACs are expressed in a restricted number of cell types.

HDAC inhibitors cause the induction of differentiation, growth arrest and/or apoptosis in a broad spectrum of transformed cells in culture and tumours in animals, including both haematological cancers and solid tumours. These inhibitory effects are believed to be caused, in part, by accumulation of acetylated proteins, such as nucleosomal histones, which appear to play a major role in regulation of gene transcription. A proposed mechanism for the anti-tumour effects of HDAC inhibitors is that the accumulation of acetylated histones leads to activation (and repression) of the transcription of a select number of genes whose expression causes inhibition of tumour cell growth. Expression profiling of cells cultured with HDAC inhibitors supports this model, as studies demonstrate that the expression of a small number of genes (2-5% of the expressed genes) is altered (activated or repressed). The mechanism of gene repression or activation is not well understood and might result from either direct or indirect effects of histone acetylation or from the increase in acetylation of proteins other than histones (e.g. transcription factors).

There is still much to be understood about the family of HDACs, including the varying functions of different HDACs and the range of HDAC substrates. The development of selective HDAC inhibitors might be important in defining their biological role and potential as therapeutic agents. Clinically, the optimal dose, timing and duration of therapy, as well as the most appropriate agents to combine with HDAC inhibitors, are still to be defined.

The compounds of this invention are useful in the inhibition of histone deacetylase. A subset of compounds of this invention is also particularly useful in the inhibition of class II histone deacetylase. The compounds are HDAC 4 and HDAC 6 inhibitors and/or active against other HDAC subtypes such as HDAC 1, 3 and 8.

The present invention provides compounds of formula I:



(I)

wherein:

m is 1, 2, 3, 4 or 5;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 1, 2, 3, 4 or 5;

t is 0 or 1;

R^1 is hydrogen, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, $N(R^a)_2$ or a ring which is: C_{3-5}cycloalkyl; C_{6-10}arylC_{1-6}alkyl; C_{6-10}aryloxy; a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2, or 3 nitrogen atoms; or a 7-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; said C_{1-6}alkyl or ring being optionally substituted by one or more groups independently chosen from $(CH_2)_vR^b$;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, -(C=O)-$N(R^a)_2$ or a ring which is: C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2, or 3 nitrogen atoms; the ring being optionally substituted by one or more groups independently selected from cyano, halogen, hydroxy, oxo, nitro, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{3-10}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{6-10}aryl;

R^3 is hydrogen; halogen; hydroxy; cyano; C_{1-6}alkyl; haloC_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkoxy; haloC_{1-6}alkoxy; C_{3-10}cycloalkyl; haloC_{3-10}cycloalkyl; C_{2-10}alkenyl; C_{6-10}alkadienyl; C_{2-10}alkynyl; nitro; $N(R^c)_2$ or a ring which is: C_{3-10}cycloalkyl; C_{5-10}cycloalkenyl; C_{6-10}aryl; C_{6-10}arylC_{1-6}alkyl; C_{6-10}aryloxy; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally bridged by a C_{1-4}alkyl group; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; the ring being optionally substituted by one or more groups independently selected from R^d;

R^4, R^6, R^7 and R^8 are independently selected from hydrogen and C_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl; or

R^5, together with N-$(CH_2)_n$-R^1 forms a piperazine ring optionally substituted by up to three substituents selected from $(CH_2)_vR^b$;

each R^a is independently hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each R^b is independently cyano, halogen, nitro, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylcarbonyl, $SO_2(NR^c)_2$, $N(R^c)_2$, or a ring which is: C_{6-10}aryl, C_{6-10}aryloxy, C_{6-10}arylcarbonyl, a 5 or 6 membered saturated heterocycle containing 1, 2 or 3 heteroatoms

independently selected from N, O and S, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; any of which rings being optionally substituted by one or more groups independently selected from cyano, halogen, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy and haloC_{1-6}alkoxy;

each R^c is independently hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, carboxy or a ring which is: C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl or C_{6-10}arylcarbonyl, the ring being optionally substituted by one or more groups independently selected from amino, hydroxy, nitro, cyano, halogen and C_{1-6}alkyl;

each R^d is independently halogen, hydroxy, oxo, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carboxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, $SO_2N(R^c)_2$, $N(R^c)_2$, SO_2R^e, $(CH_2)_w(CO)N(R^f)_2$, $O(CH_2)_yN(R^f)_2$ or a ring which is: C_{6-10}aryl; C_{6-10}arylC_{1-6}alkyl; 5 or 6 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O or S, optionally bridged by a C_{1-4}alkyl group; 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; the ring being optionally substituted by one or more groups independently selected from halogen, hydroxy, amino, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy and haloC_{1-6}alkoxy;

R^e is C_{1-6}alkyl or C_{6-10}aryl;

each R^f is independently hydrogen, C_{1-8}alkyl, aminoC_{1-8}alkyl, C_{1-6}alkylaminoC_{1-8}alkyl, di(C_{1-6}alkyl)aminoC_{1-8}alkyl, C_{1-6}alkyloxycarbonyl, C_{6-10}aryloxycarbonyl, C_{6-10}aryloxycarbonylaminoC_{1-8}alkyl or C_{6-10}arylC_{1-6}alkyloxycarbonylaminoC_{1-8}alkyl;

X is CH_2, C=O, C=O(O), (C=O)(NR^8), (C=S)(NR^8) or SO_2;

Y is S, SO or SO_2;

Z is (CH=CH), C=O, SO_2 or S;

v is 0, 1, 2, or 3;

w is 0, 1, 2 or 3; and

y is 1, 2, 3, 4, 5, 6, 7 or 8;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In an embodiment of compounds of formula I:

R^1 is hydrogen, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, $N(R^a)_2$ or a ring which is: C_{3-5}cycloalkyl; C_{6-10}arylC_{1-6}alkyl; C_{6-10}aryloxy; a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring; a 5 or 6 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2, or 3 nitrogen atoms; or a 7-10 membered saturated, partially saturated or unsaturated heterocycle

containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; said C_{1-6}alkyl or ring being optionally substituted by one or more groups independently chosen from $(CH_2)_vR^b$; and

all other variables are as defined above.

Preferably, m is 1, 2, 3 or 4. More particularly m is 1, 2 or 3.

Preferably, n is 0, 1, 2 or 3. More particularly n is 0.

Preferably, p is 0, 1, 2 or 3. More particularly p is 1.

Preferably, q is 1, 2, 3 or 4. More particularly q is 1, 2 or 3.

Preferably, R^1 is C_{1-4}alkyl, C_{1-4}alkoxy, $N(R^a)_2$ wherein R^a is independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkylcarbonyl or a ring which is: C_{3-10}cycloalkyl, phenoxy, phenyl, naphthyl, a 9-13 membered partially saturated hydrocarbon ring, a 5 or 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms or a 9-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; said alkyl or ring being optionally substituted by one or more groups independently chosen from $(CH_2)_vR^b$.

More particularly, R^1 is methyl, methoxy, $N(R^a)_2$ wherein R^a is independently selected from hydrogen, methyl and acetyl or a ring which is: indolyl, phenyl, isoquinolinyl, imidazopyridinyl, pyrrolidinyl, benzoimidazolyl, cyclopentyl, pyridazinyl, piperidinyl, morpholinyl, furyl, imidazolyl, phenoxy, quinolinyl, thiazolyl, tetrahydronaphthalenyl, dihydroindolyl, pyridinyl, naphthyl, tetrahydrobenzo[7]annulenyl, dihydroindenyl, dihydroisochromenyl, cyclohexyl, benzothiazolyl, isoxazolyl, piperazinyl, cycloheptyl, octahydroquinolizinyl, tetrahydroquinolinyl, benzoxazolyl or thienyl; said methyl or ring being optionally substituted by up to three substituents selected from $(CH_2)_VR^b$.

In one embodiment R^1 is an optionally substituted naphthyl ring.

Preferably, when R^1 is a ring it is unsubstituted or substituted by one, two or three groups independently chosen from $(CH_2)_vR^b$. More particularly, when R^1 is a ring it is unsubstituted, monosubstituted or disubstituted. In one embodiment, the R^1 ring is unsubstituted.

Preferably, v is 0, 1 or 2. More particularly, v is 0 or 1. In an embodiment v is 0.

Preferably, R^b is cyano, halogen, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, $SO_2N(R^c)_2$, $N(R^c)_2$ or a ring which is: C_{6-10}aryl, C_{6-10}arylcarbonyl, a 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; any of which rings being optionally substituted by one or more groups independently selected from halogen and C_{1-6}alkoxy groups.

More particularly, R^b is cyano, chlorine, fluorine, oxo, hydroxy, methyl, ethyl, isopropyl, methoxy, ethoxy, aminosulfonyl, acetyl, trifluoromethyl, acetylamino or a ring which is: phenyl, triazolyl,

imidazolyl, morpholinyl, pyrimidinyl, pyridinyl, benzoyl, piperidinyl or pyrrolyl; any of which rings being optionally substituted by one or more groups independently selected from chlorine and methoxy.

Preferably, when R^b is a ring it is unsubstituted or substituted by one, two or three independently selected groups. More particularly, when R^b is a ring it is unsubstituted or monosubstituted.

More particularly, R^b is phenyl, triazolyl, methyl, imidazolyl, methoxy, morpholinyl, oxo, isopropyl, pyrimidinyl, pyridinyl, fluorine, hydroxy, aminosulfonyl, benzoyl, methoxyphenyl, piperidinyl, chlorine, cyano, chlorophenyl, acetyl, trifluoromethyl, pyrrolyl, ethoxy, acetylamino or ethyl.

Thus, specific R^b groups include phenyl, 1*H*-1,2,4-triazol-1-yl, methyl, 1*H*-imidazol-4-yl, methoxy, morpholin-4-yl, oxo, isopropyl, pyrimidin-2-yl, pyridin-4-yl, fluorine, hydroxy, aminosulfonyl, benzoyl, 4-methoxyphenyl, pyridin-2-yl, piperidin-1-yl, pyridin-3-yl, chlorine, cyano, 4-chlorophenyl, acetyl, trifluoromethyl, pyrrol-1-yl, ethoxy, acetylamino and ethyl.

In one embodiment R^b is acetyl, phenyl, *iso*-propyl, hydroxy or chlorine.

R^1 groups include phenylindolyl, indolyl, triazolylphenyl, isoquinolinyl, methylimidazopyridinyl, imidazolylphenyl, phenylpyrrolidinyl, benzylpyrrolidinyl, methylindolyl, methoxybenzimidazolyl, morpholinylcyclopentyl, (oxo)(phenyl)pyridazinyl, isopropylpiperidinyl, pyrimidinylpiperidinyl, (pyridinylmethyl)piperidinyl, phenylmorpholinyl, cyclopentyl, methoxy, furyl, acetylamino, phenyl, fluorophenyl, methyphenyl, methoxyphenyl, imidazolyl, phenoxy, piperidinyl, (hydroxy)(phenyl)methyl, methylpiperidinyl, difluorophenyl, dimethylamino, quinolinyl, phenylthiazolyl, tetrahydronaphthalenyl, dihydroindolyl, pyridinyl, aminosulfonylphenyl, naphthyl, morpholinyl, benzylpiperidinyl, tetrahydrobenzo[7]annulenyl, dihydroindenyl, dihydroisochromenyl, phenylcyclohexyl, benzothiazolyl, methylisoxazolyl, morpholinylphenyl, benzylpiperazinyl, benzoylpiperazinyl, (methoxyphenyl)thiazolyl, (morpholinyl)(pyridinyl)methyl, morpholinylcycloheptyl, (phenyl)(piperidinyl)methyl, phenylpiperazinyl, octahydroquinolizinyl, benzylmorpholinyl, phenylpiperidinyl, piperidinylcyclohexyl, (piperidinyl)(pyridinyl)methyl, morpholinylcyclohexyl, tetrahydroquinolinyl, thiazolyl, biphenyl, chlorophenyl, chlorobenzoxazolyl, cyanophenyl, chlorobenzothiazolyl, (chlorophenyl)thiazolyl, acetylphenyl, methoxypyridinyl, acetylthienyl, dichlorophenyl, piperidinylcyclopentyl, trifluoromethylphenyl, (chloro)(fluoro)phenyl, dimethylphenyl, (piperidinyl)propyl, pyrrolylphenyl, (cyano)(methyl)phenyl, ethoxyphenyl, (chloro)(methoxy)phenyl and acetylaminophenyl.

In one embodiment R^1 is naphthyl, acetylphenyl, pyridinyl, phenylthiazolyl, quinolinyl, phenyl, phenylpyrrolidinyl, isopropylpiperidinyl, indolyl, (hydroxy)(phenyl)methyl, benzylpiperidinyl, dichlorophenyl, cyclopentyl, furyl or piperidinyl.

Thus, specific R^1 groups include 2-phenyl-1*H*-indol-3-yl, 1*H*-indol-3-yl, 2-(1*H*-1,2,4-triazol-1-yl)phenyl, isoquinolin-5-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, 4-(1H-imidazol-4-yl)phenyl, 3-phenylpyrrolidin-1-yl, 1-benzylpyrrolidin-3-yl, 2-methyl-1*H*-indol-3-yl, 6-methoxy-1*H*-benzimidazol-2-yl, 1-morpholin-4-ylcyclopentyl, 6-oxo-3-phenylpyridazin-1(6*H*)-yl, 1-isopropylpiperdin-4-yl, 1-pyrimidin-2-ylpiperidin-4-yl, 1-(pyridin-4-ylmethyl)piperidin-4-yl, 4-phenylmorpholin-2-yl, cyclopentyl, methoxy, 2-furyl, acetylamino, phenyl, 4-fluorophenyl, 4-methylphenyl, 3-methoxyphenyl, 1*H*-imidazol-4-yl, phenoxy, piperidin-1-yl, 1-hydroxy-1-phenylmethyl, 3-fluorophenyl, 1-methylpiperidin-4-yl, 2,4-

difluorophenyl, dimethylamino, 1*H*-imidazol-1-yl, quinolin-3-yl, 2-phenyl-1,3-thiazol-4-yl, 1,2,3,4-tetrahydronaphthalen-1-yl, 2,3-dihydro-1*H*-indol-1-yl, pyridin-3-yl, 4-(aminosulfonyl)phenyl, 1-naphthyl, morpholin-4-yl, 1-benzylpiperidin-4-yl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl, 2,3-dihydro-1*H*-inden-1-yl, 2,3-dihydro-1*H*-inden-2-yl, 1,2,3,4-tetrahydronaphthalen-2-yl, 3,4-dihydro-1*H*-isochromen-1-yl, 1-benzylpiperidin-3-yl, 1-phenylcyclohexyl, 1,3-benzothiazol-2-yl, 5-methylisoxazol-3-yl, 4-morpholin-4-ylphenyl, 4-benzylpiperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(4-methoxyphenyl)-1,3-thiazol-2-yl, 1-(morpholin-4-yl)-1-(pyridin-2-yl)methyl, 1-morpholin-4-ylcycloheptyl, 1-(phenyl)-1-(piperidin-1-yl)methyl, 4-phenylpiperazin-1-yl, (1*S*,9*aR*)-octahydro-2*H*-quinolizin-1-yl, 4-benzylmorpholin-2-yl, 4-phenylcyclohexyl, 1-phenylpiperidin-4-yl, 1-piperidin-1-ylcyclohexyl, 2-naphthyl, 1-(piperidin-1-yl)-1-(pyridin-3-yl)methyl, 1-morpholin-4-ylcyclohexyl, 3,4-tetrahydroquinolin-1(2*H*)-yl, 4-phenylpiperidin-1-yl, 1,3-thiazol-2-yl, quinolin-8-yl, quinolin-5-yl, biphenyl-4-yl, 2-chlorophenyl, 4-chlorophenyl, 5-chloro-1,3-benzoxazol-2-yl, pyridin-2-yl, pyridin-4-yl, 3-chlorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, quinolin-6-yl, 4-cyanophenyl, 2,3-dihydro-1*H*-inden-4-yl, 6-chloro-1,3-benzothiazolyl-2-yl, 4-(4-chlorophenyl)-1,3-thiazol-2-yl, 4-phenyl-1,3-thiazol-2-yl, 2-methylphenyl, 3-methylphenyl, 4-acetylphenyl, 6-methoxypyridin-3-yl, 2-acetyl-3-thienyl, 3,4-dichlorophenyl, 1-piperidin-1-ylcyclopentyl, 2-fluorophenyl, 3,5-dichlorophenyl, quinolin-2-yl, isoquinolin-3-yl, 3-acetylphenyl, 3-trifluoromethylphenyl, 3,5-difluorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methoxyphenyl, 3,4-dimethylphenyl, 2-(piperidin-1-yl)prop-2-yl, biphenyl-3-yl, 3-(1*H*-pyrrol-1-yl)phenyl, 3-(aminosulfonyl)phenyl, isoquinolin-4-yl, 1,3-benzothiazol-5-yl, 3-cyano-4-methylphenyl, 4-ethoxyphenyl, 4-chloro-3-methoxyphenyl, 3-(acetylamino)phenyl and 1,3-benzothiazol-6-yl.

In one embodiment R^1 is 2-naphthyl, 3-acetylphenyl, pyridin-3-yl, 2-phenyl-1,3-thiazol-4-yl, quinolin-3-yl, phenyl, 3-phenylpyrrolidin-1-yl, 1-isopropylpiperidin-4-yl, 1*H*-indol-3-yl, (hydroxy)(phenyl)methyl, 1-benzylpiperidin-4-yl, 3,5-dichlorophenyl, cyclopentyl, 2-furyl or piperidin-1-yl.

In another embodiment, R^1 is 2-naphthyl.

Preferably, R^2 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl; or a ring which is C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl or a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, the ring being optionally substituted by one or more groups independently selected from cyano, halogen, hydroxy, oxo or C_{1-6}alkoxy.

More particularly, R^2 is hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkyl or a phenyl, benzyl, thiophene or oxazole ring, the ring being optionally substituted by one or more C_{1-4}alkoxy groups.

Preferably, when R^2 is a ring it is unsubstituted or substituted by one or two independently selected groups. More particularly, when R^2 is a ring it is unsubstituted or monosubstituted.

Thus, particular preferred R^2 groups are hydrogen, methyl, ethyl, isopropyl, butyl, trifluoromethyl, acetoxymethyl, thienyl, phenyl, benzyl, methoxyphenyl or 1,3-oxazol-2-yl. More specifically R^2 is methyl, trifluoromethyl, acetoxymethyl, 2-thienyl, phenyl or 2-methoxyphenyl.

In an embodiment R^2 is trifluoromethyl.

Preferably, R^3 is hydrogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, $N(R^c)_2$, C_{6-10}alkadienyl or a ring which is: C_{3-7}cycloalkyl; C_{5-8}cycloalkenyl; phenyl; benzyl; phenoxy; naphthyl; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally bridged by a C_{1-2}alkyl group; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; or a 7, 8, 9 or 10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; the ring being optionally substituted by one or more groups independently selected from R^d.

More particularly, R^3 is hydrogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, $N(R^c)_2$, C_{6-10}alkadienyl or a ring which is: indolyl, benzofuranyl, chromenyl, tetrahydroisoquinolinyl, pyridinyl, naphthyl, benzodioxolyl, thienyl, thiadiazolyl, cyclopropyl, cyclohexyl, thiazolidinyl, phenyl, isoquinolinyl, cyclopentyl, bicycloheptyl, pyrazinyl, piperidinyl, napthyridinyl, quinoxalinyl, quinolinyl, pyrazolyl, dihydroisoindolyl, triazolyl, hydrobenzoxazolyl, thiazolyl, dihydrotriazolyl, dihydrobenzodioxinyl, imidazolyl, azepanyl, isoxazolyl, cyclopentenyl, pyrrolyl, cyclohexenyl, furyl, cycloheptyl, benzimidazolyl, dihydrobenzofuryl, phenoxy, tetrahydropyranyl, morpholinyl, piperazinyl, triazolopyrimidinyl, pyrrolidinyl, dihydroimidazolyl, oxazolidinyl, benzimidazolyl, azetidinyl, azabicycloheptyl, octahydroisoindolyl, benzothiadiazolyl, dihydrobenzoxazinyl, benzothienyl or dihydrobenzoxazolyl; the ring being optionally substituted by one or more groups independently selected from R^d.

In one embodiment R^3 is an optionally substituted indolyl ring.

Preferably, when R^3 is a ring it is unsubstituted or substituted by one, two, three or four independently selected R^d groups.

More particularly, when R^3 is a ring it is unsubstituted or substituted by one, two or three independently selected R^d group.

Preferably, R^d is halogen, oxo, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, haloC_{1-6}alkylcarbonyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, $N(R^c)_2$ wherein each R^c is independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkylcarbonyl; SO_2R^e wherein R^e is C_{1-4}alkyl or phenyl; $(CH_2)_w(CO)N(R^f)_2$ or $O(CH_2)_yN(R^f)_2$ wherein w is 1 or 2, y is 5, 6, 7 or 8 and each R^f is independently hydrogen, C_{1-6}alkyl, aminoC_{1-8}alkyl, C_{1-6}alkyloxycarbonyl or benzyloxycarbonylaminoC_{1-8}alkyl; or a ring which is C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, or a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; the ring being optionally substituted by one or more groups independently selected from halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

More particularly R^d is bromine, chlorine, fluorine, oxo, cyano, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, acetyl, trifluoroacetyl, methoxy, diethylamino, acetylamino, methylsulfonyl, phenylsulfonyl, [(aminohexyl)amino](oxo)ethyl, [(benzyloxycarbonylamino)hexylamino](oxo)ethyl, (butyloxycarbonylamino)hexoxy; or a phenyl, benzyl, tetrazolyl or pyrrolyl ring, the ring being optionally substituted by one or more groups independently selected from bromine, chlorine, fluorine, methyl and methoxy.

In an embodiment R^d is methyl, methoxy, oxo or tetrazolyl.

In another embodiment R^d is methyl or methoxy.

Preferably when R^d is a ring it is unsubstituted or substituted by one or two groups. More particularly, when R^d is a ring it is unsubstituted.

Particular R^3 groups are (methoxy)(methyl)indolyl, methyl, hydrogen, indolyl, benzofuranyl, oxochromenyl, tetrahydroisoquinolinyl, methylpyridinyl, naphthyl, benzodioxolyl, thienyl, thiadiazolyl, pyridinyl, trifluoromethyl, cyanocyclopropyl, cyclohexyl, oxothiazolidinyl, biphenyl, trifluoromethylcyclohexyl, isoquinolinyl, methoxyindolyl, phenylcyclopentyl, methylindolyl, cyanophenyl, (trifluoroacetyl)tetrahydroisoquinolinyl, phenyl, (phenylsulfonyl)thienyl, (dimethyl)(oxo)bicycloheptyl, cyanopyridinyl, pyrazinyl, phenylpiperidinyl, naphthyridinyl, quinoxalinyl, quinolinyl, methylpyrazolyl, methylpiperidinyl, oxodihydroisoindolyl, dimethyltriazolyl, pyrazolyl, oxohydrobenzoxazolyl, tetrazolylphenyl, thiazolyl, oxodihydrotriazolyl, dihydrobenzodioxinyl, imidazolyl, methylazepanyl, isoxazolyl, cyano, cyclopentenyl, isopropyl, methylpyrrolyl, cyclohexenyl, methylphenyl, dimethylpyrazolyl, furyl, cycloheptyl, methylthiadiazolyl, dimethylthiazolyl, chloropyridinyl, benzimidazolyl, methoxyphenyl, dimethylheptadienyl, chlorophenyl, (chloro)(fluoro)phenyl, benzoylamino, methoxybenzofuranyl, dioxodihydrobenzofuranyl, diethylaminophenyl, chlorophenoxy, bromopyridinyl, (methyl)(phenyl)isoxazolyl, methylsulfonylthienyl, dimethoxyphenyl, benzylphenyl, dimethyltetrahydropyranyl, methylimidazolyl, methylmorpholinyl, methylpiperazinyl, triazolopyrimidinyl, methylpyrrolidinyl, ethylpiperidinyl, triazolyl, oxodihydroimidazolyl, isopropylpiperazinyl, oxopyrrolidinyl, (oxo)oxazolidinyl, pyrrolidinyl, {[(aminohexyl)amino](oxo)ethyl}indolyl, [{(benzyloxycarbonylamino)hexyl]aminooxyethyl}(methoxy)(methyl)indolyl, dimethylamino, pyrrolyl, morpholinyl, piperidinyl, benzimidazolyl, [(butyloxycarbonylamino)hexoxy](methyl)indolyl, methylpyrrolidinyl, acetylpyrrolidinyl, phenylpyrrolidinyl, benzylamino, azetidinyl, methyltetrahydroisoquinolinyl, azabicycloheptyl, octahydroisoindolyl, diethylamino, isopropylpiperazinyl, (acetylamino)(methyl)thiazolyl, chlorothienyl, dimethylisoxazolyl, benzothiadiazolyl, methyldihydrobenzoxazinyl, cyclopentyl, dimethylimidazolyl, benzothienyl, methylazetidinyl, piperazinyl, triisopropylphenyl, (bromo)(dichloro)thienyl, dichlorophenyl, trichlorophenyl, trifluoromethoxyphenyl, (chloro)(methoxy)phenyl, (chloro)(dimethyl)pyrazolyl, (chloro)(cyano)phenyl, pyrrolylphenyl and (oxo)dihydrobenzoxazolyl. A further particular R^3 group is *tert*-butoxy.

In one embodiment R^3 is (methoxy)(methyl)indolyl, methyl, benzoylamino, cyano, oxohydrobenzoxazolyl, *tert*-butoxy, thienyl, imidazolyl, isopropyl, methylpiperazinyl, methylpiperidinyl, pyridinyl, phenyl, pyrazolyl, dimethylamino, quinoxalinyl or tetrazolylphenyl.

In another embodiment R^3 is methylmethoxyindolyl.

Thus, specific R^3 groups include 5-methoxy-2-methyl-1*H*-indol-3-yl, hydrogen, methyl, 1*H*-indol-3-yl, benzofuran-2-yl, 4-oxo-4*H*-chromen-3-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 2-methylpyridin-3-yl, 1-naphthyl, 1,3-benzodioxol-5-yl, 3-thienyl, 1,2,3-thiadiazol-4-yl, pyridin-3-yl, trifluoromethyl, 1-cyanocyclopropyl, cyclohexyl, 2-oxo-1,3-thiazolidin-4-yl, biphenyl-4-yl, 4-trifluoromethylcyclohexyl, isoquinolin-3-yl, 5-methoxy-1*H*-indol-2-yl, 1-phenylcyclopentyl, 2-methyl-1*H*-indol-3-yl, 1-methyl-1*H*-indol-3-yl, 2-naphthyl, isoquinolin-1-yl, 1*H*-indol-5-yl, 4-cyanophenyl, 3-cyanophenyl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, phenyl, 5-(phenylsulfonyl)-2-thienyl, 7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl, 6-cyanopyridin-3-yl, pyrazin-2-yl, 6-phenylpiperidin-2-yl, 1,8-naphthyridin-2-yl, 1,6-naphthyridin-2-yl, biphenyl-3-yl, quinoxalin-6-yl, isoquinolin-4-yl, quinolin-5-yl, 3-methyl-1*H*-pyrazol-1-yl, 1-methyl-1*H*-pyrazol-3-yl, 1-methylpiperidin-2-yl, 3-oxo-2,3-dihydro-1*H*-isoindol-1-yl, 3,5-dimethyl-1*H*-1,2,4-triazol-1-yl, 1*H*-pyrazol-4-yl, 2-oxo-1,3-benzoxazol-3(2*H*)-yl, 4-(1*H*-tetrazol-1-yl)phenyl, 3-(1*H*-tetrazol-1-yl)phenyl, 2-(1*H*-tetrazol-1-yl)phenyl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1*H*-pyrazol-3-yl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl, 1*H*-pyrazol-1-yl, 2,3-dihydro-1,4-benzodioxin-2-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 1-methylazepan-2-yl, isoxazol-3-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, cyano, cyclopenten-3-yl, isopropyl, pyridin-2-yl, pyridin-4-yl, biphenyl-2-yl, isoxazol-4-yl, 1-methyl-1*H*-pyrrol-2-yl, cyclohexen-1-yl, 2-thienyl, 3-methylphenyl, 5-methylpyridin-2-yl, 1,5-dimethyl-1*H*-pyrazol-3-yl, 2-furyl, cycloheptyl, 4-methyl-1,2,3-thiadiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 2-chloropyridin-3-yl, 1*H*-benzimidazol-6-yl, 4-methoxyphenyl, 2,6-dimethyl-1,5-heptadien-1-yl, pyridin-4-yl, 4-chlorophenyl, 2-chloro-4-fluorophenyl, benzoylamino, 7-methoxy-1-benzofuran-2-yl, 1,3-dioxo-1,3-dihydro-2-benzofuran-5-yl, 4-oxo-4*H*-chromen-2-yl, 4-(diethylamino)phenyl, 4-chlorophenoxy, 5-bromopyridin-3-yl, 5-methyl-3-phenylisoxazol-4-yl, 5-methylsulfonyl-2-thienyl, 3,5-dimethoxyphenyl, 2-benzylphenyl, 1,2,5-thiadiazol-3-yl, 2,2,-dimethyltetrahydro-2*H*-pyran-4-yl, 1-methyl-1*H*-imidazo-2-yl, 4-methylmorpholin-3-yl, 1-methyl-1*H*-pyrazol-4-yl, 4-methylpiperazin-1-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, quinolin-8-yl, 1-methylpyrrolidin-3-yl, 1-ethylpiperidin-3-yl, 1*H*-1,2,3-triazol-4-yl, 2-oxo-2,3-dihydro-1*H*-imidazol-4-yl, 4-isopropylpiperazin-1-yl, 1-ethylpiperidin-2-yl, 5-oxopyrrolidin-2-yl, 2-oxo-1,3-oxazolidin-3-yl, quinolin-4-yl, 4-methylmorpholin-2-yl, pyrrolidin-1-yl, 1-{2-[(6-aminohexyl)amino]-2-oxoethyl}-1*H*-indol-3-yl, 1-{2-[6-(benzyloxycarbonylamino)hexyl]amino-2-oxoethyl}-5-methoxy-2-methyl-*1H*-indol-3-yl, dimethylamino, 1*H*-pyrrol-2-yl, morpholin-2-yl, 1*H*-imidazol-4-yl, piperidin-3-yl, piperidin-1-yl, 1*H*-benzimidazol-2-yl, L-pyrrolidin-2-yl, *D*-pyrrolidin-2-yl, 5-[6-(*tert*-butyloxycarbonylamino)hexoxy]-2-methyl-1*H*-indol-3-yl, (2*S*)-piperidin-2-yl, (2*R*)-piperidin-2-yl, 1-methyl-*L*-pyrrolidin-2-yl, 1-methyl-*D*-pyrrolidin-2-yl, 1-methyl-*L*-piperidin-3-yl, 1-methyl-*D*-piperidin-3-yl, 1-acetyl-*L*-pyrrolidin-2-yl, 1-acetyl-*D*-pyrrolidin-2-yl, 1-methylpiperidin-4-yl, (2*S*)-1-methylpiperidin-2-yl, (2*R*)-1-methylpiperidin-2-yl, 4-methylpiperazin-2-yl, (5*S*)-5-phenyl-*D*-pyrrolidin-2-yl, (5*R*)-1-phenyl-*D*-pyrrolidin-2-yl, benzylamino, 4-phenylpiperidin-

2-yl, 5-phenylpiperidin-2-yl, 3-phenylpiperidin-2-yl, (2*R*)-azetidin-2-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl, 2-azabicyclo[2.2.1]hept-2-yl, octahydro-1*H*-isoindol-1-yl, diethylamino, 1-methylpiperidin-3-yl, 3-thienyl, 4-isopropylpiperazin-1-yl, 1-methylpiperidin-2-yl, 2-(acetylamino)-4-methyl-1,3-thiazol-5-yl, 5-chloro-2-thienyl, 3,5-dimethylisoxazol-4-yl, 2,1,3-benzothiadiazol-4-yl, 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl, cyclopentyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 3-methoxyphenyl, 1,2-dimethyl-1*H*-imidazol-4-yl, 1-benzothien-3-yl, piperazin-1-yl, 2,4,6-triisopropylphenyl, 4-bromo-2,5-dichlorothien-3-yl, 3,5-dichlorophenyl, 2,4,6-trichlorophenyl, 4-trifluoromethoxyphenyl, 5-chloro-2-methoxyphenyl, 5-chloro-1,3-dimethylpyrazol-4-yl, 2-chloro-4-cyanophenyl, isoquinolin-5-yl, 1,4-quinoxalin-6-yl, pyrazol-4-yl and 2-(1*H*-pyrrol-1-yl)phenyl. A further particular R^3 group is *tert*-butoxy.

In one embodiment R^3 is 5-methoxy-2-methyl-1*H*-indol-3-yl, methyl, benzoylamino, cyano, 2-oxo-1,3-benzoxazol-3(2H)-yl, *tert*-butoxy, 3-thienyl, 1*H*-imidazol-2-yl, isopropyl, 4-methylpiperazin-1-yl, 1-methylpiperidin-4-yl, pyridin-3-yl, phenyl, 1*H*-pyrazol-4-yl, dimethylamino, quinoxalin-6-yl or 2-(1*H*-tetrazol-1-yl)phenyl.

In another embodiment, R^3 is 5-methoxy-2-methyl-1*H*-indol-3-yl.

Preferably, R^4 is hydrogen or C_{1-4}alkyl. More particularly, R^4 is hydrogen or methyl. In one embodiment R^4 is hydrogen.

Preferably, R^5 is hydrogen or C_{1-4}alkyl. In one embodiment R^5 is hydrogen.
In another embodiment, R^5 together with N-$(CH_2)_nR^1$ forms a piperazine ring substituted by C_{1-6}alkyl, particularly methyl or ethyl. In another embodiment, R^5 together with N-$(CH_2)_nR^1$ represents 4-ethylpiperazin-1-yl.

Preferably, R^6 and R^7 are independently selected from hydrogen or methyl. In one embodiment one of R^6 and R^7 is hydrogen and the other methyl. In another embodiment R^6 and R^7 are both hydrogen.

Preferably, R^8 is hydrogen or methyl. In one embodiment R^8 is hydrogen.

Preferably, each R^a is independently hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl. More particularly each R^a is independently hydrogen, methyl or acetyl.

Preferably, when R^c is a ring it is unsubstituted or substituted by one, two or three independently selected groups.

Preferably, each R^c is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}arylC_{1-6}alkyl or C_{6-10}arylcarbonyl. More particularly, each R^c is independently hydrogen, methyl, ethyl, acetyl, benzyl or benzoyl. In one embodiment each R^c is hydrogen. In another embodiment each R^c is methyl or benzoyl.

Preferably, R^e is C_{1-4}alkyl or phenyl. More particularly, R^e is methyl or phenyl.

Preferably, each R^f is hydrogen, C_{1-6}alkyl, aminoC_{1-8}alkyl, C_{1-6}alkyloxycarbonyl or benzyloxycarbonylaminoC_{1-6}alkyl. More particularly, each R^f is hydrogen, aminohexyl, butyloxycarbonyl or benzyloxycarbonylaminohexyl.

In an embodiment X is CH_2, C=O, C=O(O), (C=O)(NH), (C=S)(NH) or SO_2.

In another embodiment X is CH_2, C=O or SO_2.

In another embodiment X is CH_2. In another embodiment X is C=O. In another embodiment X is. SO_2.

In one embodiment Y is S. In another embodiment Y is SO. In another embodiment Y is SO_2.

In one embodiment Z is (CH=CH). In another embodiment Z is C=O. In another embodiment Z is SO_2. In another embodiment Z is S.

In another embodiment Z is C=O or SO_2.

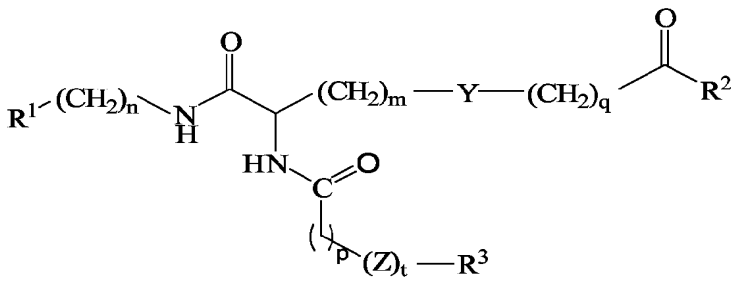
In one embodiment t is 0. In another embodiment t is 1.

Preferably, w is 0, 1, 2 or 3. More particularly, w is 1 or 2. Favourably, w is 1.

Preferably, y is 5, 6, 7 or 8. More particularly, y is 5, 6 or 7. Favourably y is 6.

Preferably, the α1 carbon asymmetric centre of the compounds of the present invention has the stereochemical configuration of S.

The present invention also provides compounds of formula IA:



(IA)

wherein:

m is 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 1, 2 or 3;

t is 0 or 1;

R^1 is C_{1-4}alkyl, C_{1-4}alkoxy, $N(R^a)_2$ wherein R^a is independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkylcarbonyl or a ring which is: C_{3-10}cycloalkyl, phenoxy, phenyl, naphthyl, a 9-13 membered partially saturated hydrocarbon ring, a 5 or 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms or a 9-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; said alkyl or ring being optionally substituted by one, two or three groups independently chosen from $(CH_2)_vR^b$;

R^2 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl; or a ring which is C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl or a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, the ring being optionally substituted by one, two or three groups independently selected from cyano, halogen, hydroxy, oxo or C_{1-6}alkoxy;

R^3 is hydrogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, $N(R^c)_2$, C_{6-10}alkadienyl or a ring which is: C_{3-7}cycloalkyl; C_{5-8}cycloalkenyl; phenyl; benzyl; phenoxy; naphthyl; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally bridged by a C_{1-2}alkyl group; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; or a 7, 8, 9 or 10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; the ring being optionally substituted by one, two or three groups independently selected from R^d;

v is 0 or 1;

each R^b is independently cyano, halogen, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, $SO_2N(R^c)_2$, $N(R^c)_2$ or a ring which is: C_{6-10}aryl, C_{6-10}arylcarbonyl, a 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; any of which rings being optionally substituted by one, two or three groups independently selected from halogen and C_{1-6}alkoxy;

each R^c is independently hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}arylC_{1-6}alkyl or C_{6-10}arylcarbonyl;

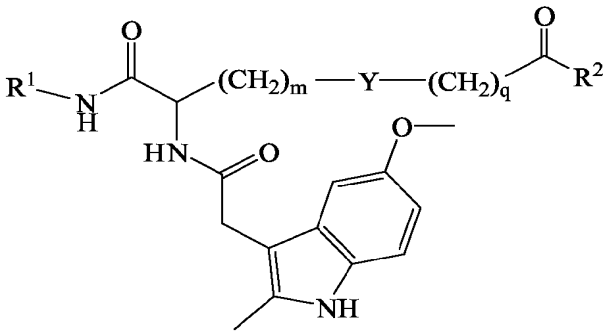
each R^d is independently bromine, chlorine, fluorine, oxo, cyano, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, acetyl, trifluoroacetyl, methoxy, diethylamino, acetylamino, methylsulfonyl, phenylsulfonyl, [(aminohexyl)amino](oxo)ethyl, [(benzyloxycarbonylamino)hexylamino](oxo)ethyl, (butyloxycarbonylamino)hexoxy; or a phenyl, benzyl, tetrazolyl or pyrrolyl ring, the ring being optionally substituted by one, two or three groups independently selected from bromine, chlorine, fluorine, methyl and methoxy;

Y is S, SO or SO_2; and

Z is C=O or SO_2;

or a pharmaceutically acceptable salt or stereoisomer thereof.

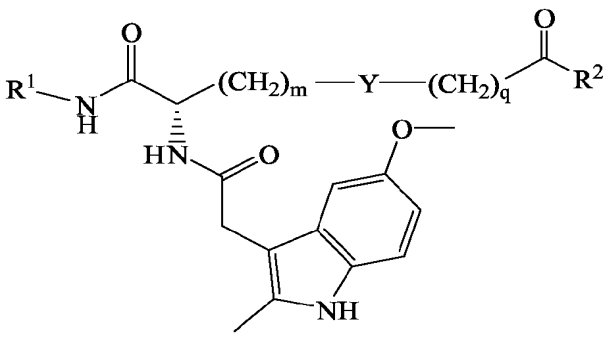
The present invention also provides compounds of formula IB:



(IB)

wherein m, q, R^1, R^2 and Y are as defined above;
or a pharmaceutically acceptable salt or stereoisomer thereof.

A favoured class of compounds of the present invention have the stereochemical configuration of formula IC:



(IC)

wherein, m, q, R^1 R^2 and Y are as defined for formula IB.
or a pharmaceutically acceptable salt thereof.

The preferences for identities in formulae IA, IB and IC are as defined for formula I, *mutatis mutandis*.

The present invention also includes within its scope N-oxides of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula I and salts thereof, for example, hydrates.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

The compounds may exist in different isomeric forms, all of which are encompassed by the present invention.

When any variable (e.g. R^a and R^b, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted" should be taken to be equivalent to the phrase "unsubstituted or substituted with one or more substituents" and in such cases the preferred embodiment will have from zero to three substituents. More particularly, there are zero to two substituents. A substituent on a saturated, partially saturated or unsaturated heterocycle can be attached at any substitutable position.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example,"C_{1-6}alkyl" is defined to include groups having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement. For example, "C_{1-6}alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, and so on. The preferred alkyl group is methyl. The term "cycloalkyl" means a monocyclic, bicyclic or polycyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For

example, "C_{3-10}cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" as defined in this embodiment includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl, 7,7-dimethylbicyclo[2.2.1]heptyl and so on. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl above. Examples of suitable alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy and *t*-butoxy. The preferred alkoxy group is methoxy.

The terms "haloC_{1-6}alkyl" and "haloC_{1-6}alkoxy" mean a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC_{1-6}alkyl and fluoroC_{1-6}alkoxy groups, in particular fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CHF_2, CH_2F, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, $OCHF_2$, OCH_2F, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and $OCHF_2$. The term 'haloC_{3-10}cycloakyl' can be construed analogously.

The term "hydroxyC_{1-6}alkyl" means a C_{1-6}alkyl group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by hydroxy groups. Preferred are CH_2OH, CH_2CHOH and $CHOHCH_3$.

As used herein, the term "C_{1-6}alkylcarbonyl" or "C_{1-6}alkoxycarbonyl" denotes a C_{1-6}alkyl or C_{1-6}alkoxy radical, respectively, attached via a carbonyl (C=O) radical. Suitable examples of C_{1-6}alkylcarbonyl groups include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl and *tert*-butylcarbonyl. Examples of C_{1-6}alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and *tert*-butoxycarbonyl. The term 'C_{6-10}arylcarbonyl' can be construed analogously, and an example of this group is benzoyl.

The term "C_{1-6}alkylcarbonyloxyC_{1-6}alkyl" denotes a C_{1-6}alkylcarbonyl radical attached via a oxyC_{1-6}alkyl group, for example $-CH_2O(C=O)CH_3$ or $-CH_2O(C=O)CH_2CH_3$. The terms 'C_{6-10}aryloxycarbonylaminoC_{1-8}alkyl' and 'C_{6-10}arylC_{1-6}alkyloxycarbonylaminoC_{1-8}alkyl' can be constued analogously.

As used herein, the term "C_{2-10}alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Alkenyl groups include ethenyl, propenyl, butenyl and 2-methylbutenyl. The straight or branched portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated. Preferred alkenyl groups include ethenyl and propenyl. The term 'C_{5-10}cycloalkenyl' can be construed analogously.

The term "C_{6-10}alkadienyl" refers to a hydrocarbon radical, straight or branched, containing from 5 to 10 carbon atoms and two carbon to carbon double bonds.

The term "C_{2-10}alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight or branched portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated. Preferred alkynyl groups include ethynyl and propynyl

As used herein, "C_{6-10}aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of 6 to 10 atoms, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and tetrahydrobenzo[7]annulene. The preferred aryl group is phenyl or naphthyl, especially phenyl.

The terms 'C_{6-10}arylC_{1-6}alkyl' and 'C_{6-10}aryloxy' denote a C_{6-10}aryl radical linked via an alkyl and oxygen bridge, respectively.

Examples of particular heterocycles of this invention are benzimidazolyl, benzofurandionyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, benzoxazolonyl, benzothiazolyl, benzothiadiazolyl, benzodioxolyl, benzoxadiazolyl, benzoisoxazolyl, benzoisothiazolyl, chromenyl, chromanyl, isochromanyl, carbazolyl, carbolinyl, cinnolinyl, epoxidyl, furanyl, furazanyl, imidazolyl, indolinyl, indolyl, indolizinyl, indolinyl, isoindolinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazolinyl, isoxazolinyl, oxetanyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridinyl, pyrimidinyl, triazinyl, tetrazinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinolizinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidyl, pyridin-2-onyl, pyrrolidinyl, imidazolinyl, pyrazolinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydroisoquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dihydroisochromenyl, dihydroimidazolonyl, dihydrotriazolonyl, dihydrobenzodioxinyl, dihydrothiazolopyrimidinyl, dihydroimidazopyrazinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolinyl, thiazolidinonyl, imidazolonyl, isoindolinonyl, octahydroquinolizinyl, octahydroisoindolyl, imidazopyridinyl, azabicycloheptanyl, chromenonyl, triazolopyrimidinyl, dihydrobenzoxazinyl, thiazolotriazolyl, azoniabicycloheptanyl, azoniabicyclooctanyl, phthalazinyl, naphthyridinyl, quinazolinyl, pteridinyl and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

Preferred 5 or 6 membered saturated or partially saturated hetereocycles are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azoniabicyclo[2.2.1]heptanyl and azoniabicyclo[2.2.2]octanyl.

A preferred 7 membered saturated ring is diazepanyl.

Preferred 5 membered unsaturated heterocycles are thienyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, thiadiazolyl, oxazolyl, triazolyl and oxadiazolyl.

A preferred 6 membered unsaturated heterocycle is pyridinyl or pyrimidinyl.

Preferred 6-13 membered saturated, partially saturated or unsaturated hydrocarbon rings are cyclohexyl, phenyl, naphthyl, tetrahydronaphthalenyl, dihydroindenyl, fluorenyl, adamantyl and tetrahydrobenzo[7]annulenyl, particularly naphthyl.

Preferred 7-10 membered saturated, partially saturated or unsaturated heterocyclic rings are dihydroquinolinyl, quinolinyl, indolyl, imidazopyridinyl, benzothiazolyl, quinoxalinyl, benzothiadiazolyl, benzoxazolyl, dihydrobenzodioxinyl, benzotriazolyl, benzodioxolyl, dihydroisoindolyl, dihydroindolyl, dihydroisoquinolinyl, isoquinolinyl, benzoisothiazolyl and dihydroimidazopyrazinyl, particularly indolyl.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

Particular compounds within the scope of the present invention are:

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-*S*-(4-oxopentyl)-*L*-cystein amide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-3-[(4-oxopentyl)sulfinyl]-L-alaninamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-3-[(4-oxopentyl)sulfonyl]-L-alaninamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-*S*-(3-oxobutyl)-*L*-homocysteinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)thio]-L-norvalinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-*L*-norvalinamide;

(2*S*)-2-{[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]amino}-*N*-2-naphthyl-4-[(3-oxobutyl)sulfonyl]butanamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)sulfinyl]-*L*-norvalinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)sulfonyl]-*L*-norvalinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(3-Acetoxy-2-oxopropyl)thio]-*L*-norvalinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-{[2-oxo-2-(2-thienyl)ethyl]thio}-*L*-norvalinamide;

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxo-2-phenylethyl)thio]-*L*-norvalinamide; and

N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-5-{[2-(2-methoxyphenyl)-2-oxoethyl]thio}-*N*^{1}-2-naphthyl-*L*-norvalinamide;

and the pharmaceutically acceptable free bases, salts and stereoisomers thereof.

Further particular compounds within the scope of the present invention are:

N^2-Acetyl-N-(3-acetylphenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-Benzoylglycyl-N-(3-acetylphenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(3-Acetylphenyl)-N^2-(cyanoacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(3-Acetylphenyl)-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(3-Acetylphenyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
tert-Butyl {(1S)-1-[(pyridin-3-ylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate;
tert-Butyl {(1S)-1-[(2-naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate;
N^2-(tert-Butoxycarbonyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
tert-Butyl {(1S)-1-{[(3-acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate;
N-(3-Acetylphenyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(3-Acetylphenyl)-N^2-(1H-imidazol-2-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-Benzoylglycyl-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-(4-Methylpentanoyl)-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-Acetyl-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-2-Naphthyl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-[(4-Methylpiperazin-1-ium-1-yl)acetyl]-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-(4-Methylpentanoyl)-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-[(1-Methylpiperidinium-4-yl)carbonyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate);
N-{(1S)-1-[(2-Naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;
N^2-Acetyl-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-Pyridinium-3-yl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-(1H-Imidazol-3-ium-2-ylcarbonyl)-N-(quinolin-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-[(Methylsulfonyl)acetyl]-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-Benzoylglycyl-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-Acetyl-N-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-Benzoylglycyl-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-2-Naphthyl-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-(4-Methylpentanoyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-[(Methylsulfonyl)acetyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-(Phenylacetyl)-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-[(2-Phenyl-1,3-thiazol-4-yl)methyl]-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-(Phenylacetyl)-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-[(1-Methylpiperidinium-4-yl)carbonyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate);

N^2-(Phenylacetyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-[(2-Phenyl-1,3-thiazol-4-yl)methyl]-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-2-Naphthyl-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide,

N-[2-(3-Phenylpyrrolidinium-1-yl)ethyl]-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(Quinolinium-3-ylmethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-[2-(1-Isopropylpiperidinium-4-yl)ethyl]-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-(4-Methylpentanoyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-Acetyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-(Phenylacetyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-[(Dimethylammonio)acetyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate);
N-Benzoylglycyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;
N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide;
N-{(1*S*)-1-({[2-(1*H*-indol-3-yl)ethyl]amino}carbonyl)-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide;
N^2-Acetyl-N-(2-hydroxy-2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-Acetyl-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}-2-(1H-tetrazol-1-yl)benzamide;
N^2-[(Methylsulfonyl)acetyl]-N-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1S)-1-{[(2-Hydroxy-2-phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;
N-2-Naphthyl-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-[2-(1H-Indol-3-yl)ethyl]-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1*S*)-1-{[(2-Phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;
N^2-(1H-Imidazol-2-ylcarbonyl)-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1S)-1-({[(2-Phenyl-1,3-thiazol-4-yl)methyl]amino}carbonyl)-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide;
N^2-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
2-({(1S)-1-{[(2-Hydroxy-2-phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate;
N-{(1S)-1-[(2-Naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide;
N-(Quinolinium-3-ylmethyl)-N^2-[2-(1H-tetrazol-1-yl)benzoyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-(2-Phenylethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-(5-Oxo-5-phenylpentanoyl)-N-[(2-phenyl-1,3-79thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-(Cyanoacetyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(2-Hydroxy-2-phenylethyl)-N^2-(1H-imidazol-2-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-Benzoylglycyl-N-(2-hydroxy-2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(2-Hydroxy-2-phenylethyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(2-Hydroxy-2-phenylethyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(1-Benzylpiperidinium-4-yl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(3,5-Dichlorophenyl)-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(1-Benzylpiperidinium-4-yl)-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-Cyclopentyl-N^2-[(4-methylpiperazin-1-ium-1-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(3,5-Dichlorophenyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(1-Benzylpiperidinium-4-yl)-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(1-Benzylpiperidinium-4-yl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

2-({(1S)-1-{[(2-Furylmethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate;

N-(2-Furylmethyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-{(1S)-1-[(Cyclopentylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;

N-Benzoylglycyl-N-(1-benzylpiperidinium-4-yl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-[(Methylsulfonyl)acetyl]-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(1-Benzylpiperidinium-4-yl)-N^2-(4-methylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-Acetyl-N-(3,5-dichlorophenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N-(3,5-Dichlorophenyl)-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;

N^2-(5-Oxo-5-phenylpentanoyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N-(3,5-Dichlorophenyl)-N^2-[(1-methylpiperidinium-4-yl)carbonyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;

N^2-(4-Methylpentanoyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-Acetyl-N-cyclopentyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-Cyclopentyl-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-{(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide;
N-Cyclopentyl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(1-Benzylpiperidinium-4-yl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-(Cyanoacetyl)-N-cyclopentyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(2-Piperidinium-1-ylethyl)-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-(2-Piperidinium-1-ylethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-Acetyl-N-(1-benzylpiperidinium-4-yl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-Benzoylglycyl-N-(3,5-dichlorophenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(1-Benzylpiperidinium-4-yl)-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
N-(3,5-Dichlorophenyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(3,5-Dichlorophenyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
2-({(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate;
N-{(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide;
N-Benzoylglycyl-N-(2-furylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N-(1-Benzylpiperidinium-4-yl)-N^2-[(1-methylpiperidinium-4-yl)carbonyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate);
N-Cyclopentyl-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide;
N^2-(Phenylacetyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate;
and the pharmaceutically acceptable free bases, salts and stereoisomers thereof.

Included in the instant invention is the free base of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the specific compounds exemplified herein are the protonated salts of amine compounds. Compounds of Formula I with a

heterocycle ring containing 2 or more N atoms may be protonated on any one, some or all of the N atoms. The term "free base" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. Preferably, a pharmaceutically acceptable salt of this invention contains 1 equivalent of a compound of formula (I) and 1, 2 or 3 equivalent of an inorganic or organic acid. More particularly, pharmaceutically acceptable salts of this invention are the trifluoroacetate or the chloride salts, especially the trifluoroacetate salts.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, *N*,*N*^{1}-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine,

lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.* (1977) **66**:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The compounds of the invention can be used in a method of treatment of the human or animal body by therapy.

The compounds of the invention find use in a variety of applications for human and animal health. The compounds of the invention are histone deacetylase (HDAC) inhibitors useful in the treatment of cancer among other diseases. HDACs catalyse the removal of acetyl groups from lysine residues on proteins, including histones and HDAC inhibitors show diverse biological functions including affecting gene expression, cell differentiation, cell cycle progression, growth arrest, and/or apoptosis. See *J. Med. Chem.* (2003) **46**:5097 and *Curr. Med. Chem.* (2003) **10**:2343.

The compounds of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), neurodegenerative diseases, schizophrenia and stroke

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone:

osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating cellular proliferation diseases.

The present invention also provides a method for the treatment of cellular proliferation diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the instant invention may also be useful in the treatment or prevention of neurodegenerative diseases, including, but not limited to, polyglutamine-expansion-related neurodegeneration, Huntington's disease, Kennedy's disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), protein-aggregation-related neurodegeneration, Machado-Joseph's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spongiform encephalopathy, a prion-related disease and multiple sclerosis (MS). See WO 02/090534 and WO 03/083067.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating or preventing neurodegenerative diseases.

The present invention also provides a method for treating or preventing neurodegenerative diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of mental retardation, in particular "X chromosome-linked mental retardation" and "Rubinstein-Taybi syndrome".

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing mental retardation.

The present invention also provides a method for treating or preventing mental retardation, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of schizophrenia, see WO 02/090534.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing schizophrenia.

The present invention also provides a method for treating or preventing schizophrenia, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of inflammatory diseases, including, but not limited to stroke. See Leoni *et al* (2002), *PNAS*, **99(5)**:2995-3000, Suuronen *et al.*(2003) *J. Neurochem*, **87**:407-416 and *Drug Discovery Today* (2005), **10**:197-204.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing inflammatory diseases.

The present invention also provides a method for treating or preventing inflammatory diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the present invention are also useful in the inhibition of smooth muscle cell proliferation and/or migration and are thus useful in the prevention and/or treatment of restenosis, for example after angioplasty and/or stent implantation.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing restenosis.

The present invention also provides a method for treating or prevention restenosis, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

In one embodiment, smooth muscle cell proliferation and/or migration is inhibited and restenosis is prevented and/or treated by providing a stent device having one or more of the compounds of the instant invention in or on the stent device, e.g. coated onto the stent device. The stent device is designed to controllably release the compounds of the invention, thereby inhibiting smooth miscle cell proliferation and/or migration and preventing and/or treating restenosis.

Stenosis and restenosis are conditions associated with a narrowing of blood vessels. Stenosis of blood vessels generally occurs gradually over time. Restenosis, in contrast, relates to a narrowing of

blood vessels following an endovascular procedure, such as balloon angioplasty and/or stent implantation, or a vascular injury.

Balloon angioplasty is typically performed to open a stenotic blood vessel; stenting is usually performed to maintain the patency of a blood vessel after, or in combination with, balloon angioplasty. A stenotic blood vessel is opened with balloon angioplasty by navigating a balloon-tipped catheter to the site of stenosis, and expanding the balloon tip effectively to dilate the occluded blood vessel. In an effort to maintain the patency of the dilated blood vessel, a stent may be implanted in the blood vessel to provide intravascular support to the opened section of the blood vessel, thereby limiting the extent to which the blood vessel will return to its occluded state after release of the balloon catheter. Restenosis is typically caused by trauma inflicted during angioplasty, effected by, for example, ballon dilation, atherectomy or laser ablation treatment of the artery. For these procedures, restenosis occurs at a rate of about 30% to about 60% depending on the vessel location, lesion length and a number of other variables. This reduces the overall success of the relatively non-invasive balloon angioplasty and stenting procedures

Restenosis is attributed to many factors, including proliferation of smooth muscle cells (SMC). SMC proliferation is triggered by the initial mechanical injury to the intima that is sustained at the time of balloon angioplasty and stent implantation. The process is characterized by early platelet activation and thrombus formation, followed by SMC recruitment and migration, and, finally, cellular proliferation and extracellular matrix accumulation. Damaged endothelial cells, SMCs, platelets, and macrophages secrete cytokines and growth factors which promote restenosis. SMC proliferation represents the final common pathway leading to neointimal hyperplasia. Therefore, anti-proliferative therapies aimed at inhibiting specific regulatory events in the cell cycle may constitute the most reasonable approach to restenosis after angioplasty.

The compounds of the invention may also be used as immunosuppressants or immunomodulators and can accordingly be used in the treatment or prevention of immune response or immune-mediated responses and diseases such as systemic lupus erythematosus (SLE) and acute or chronic transplant rejection in a recipient of an organ, tissue or cell transplant, (see WO O5/013958).

Examples of autoimmune diseases for which the compounds of the invention may be employed include autoimmune hematological disorders (including hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, thyroiditis, Hashimoto's thyroiditis, polychondritis, sclerodoma, Wegener granulamatosis,dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, atopic dermatitis, vasculitis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), diabetes type II and the disorders associated therewith, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis,glomerulonephritis (with and without nephrotic syndrome, including idiopathic nephrotic syndrome or minimal change nephropathy), juvenile dermatomyositisinfectious, auto-antibody

mediated diseases, aplastic anemia, Evan's syndrome, autoimmune hemolytic anemia, infectious diseases causing aberrant immune response and/or activation, such as traumatic or pathogen induced immune disregulation, including for example, that which are caused by hepatitis B and C infections, staphylococcus aureus infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by inflammatory response (e.g. leprosy); and circulatory diseases, such as arteriosclerosis, atherosclerosis, polyarteritis nodosa and myocarditis.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for the treatment or prevention of immune disorders.

The present invention also provides a method of treating or preventing immune disorders, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of other diseases such as diabetes, cardiovascular disorders, asthma, cardiac hypertrophy and heart failure, (see *Cell* (2002), **110**:479-488).

The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or

hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils,

mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration generally occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. Thus, this invention provides combinations of compounds of formula (I) and known therapeutic agents and/or anti-cancer agents for simultaneous, separate or sequential administration. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

Examples of "other HDAC inhibitors" include suberoylanilide hydroxamic acid (SAHA), LAQ824, LBH589, PXD101, MS275, FK228, valproic acid, butyric acid and CI-994.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2*H*-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-*N*-(4'-hydroxyphenyl) retinamide, and *N*-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin, bortezomib, epoxomicin and peptide aldehydes such as MG 132, MG 115 and PSI.

In an embodiment, the compounds of the present invention may be used in combination with other HDAC inhibitors such as SAHA and proteasome inhibitors.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-*N*-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, *N*,*N*-dimethyl-*L*-valyl-*L*-valyl-*N*-methyl-*L*-valyl-L-prolyl-*L*-proline-*t*-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-*N*,*N*-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6*H*) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1*H*,12*H*-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9*H*,15*H*)dione, lurtotecan, 7-[2-(*N*-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, *N*-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide, asulacrine, (5*a*, 5*aB*, 8*aa*,9*b*)-9-[2-[*N*-[2-(dimethylamino)ethyl]-*N*-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5*a*,6,8,8*a*,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[*c*]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6*H*-pyrazolo[4,5,1-de]acridin-6-one, *N*-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9*H*-thioxanthen-4-ylmethyl]formamide, *N*-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7*H*-indeno[2,1-*c*] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768, WO 01/98278, WO 02/056880, WO 03/050,064, WO 03/050,122, WO 03/049,527, WO 03/049,679, WO 03/049,678, WO 03/039460 , WO 03/079973, WO 03/099211, WO 2004/039774, WO 03/105855, WO 03/106417, WO 2004/087050, WO 2004/058700, WO 2004/058148 and WO 2004/037171 and US applications US 2004/132830 and US 2004/132719. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, *N*-[5-(2,3-dihydro-benzofuryl)sulfonyl]-*N*'-(3,4-dichlorophenyl)urea, *N*6-[4-deoxy-4-[*N*2-[2(E),4(E)-tetradecadienoyl]glycylamino]-*L*-glycero-*B*-*L*-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*-pyrimidino[5,4-b][1,4]thiazin-6-yl-(*S*)-ethyl]-2,5-thienoyl-*L*-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-*N*4-palmitoyl-1-*B*-*D*-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359.

For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer* (1999), **35(9)**:1394-1401.

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine

kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS* (1992) **89**:7384; *JNCI* (1982) **69**:475; *Arch. Opthalmol.* (1990) **108**:573; *Anat. Rec.* (1994) **238**:68; *FEBS Letters* (1995) **372**:83; *Clin, Orthop.*(1995) **313**:76; *J. Mol. Endocrinol.* (1996) **16**:107; *Jpn. J. Pharmacol.* (1997) **75**:105; *Cancer Res.*(1997) **57**:1625 (1997); *Cell* (1998) **93**:705; *Intl. J. Mol. Med.* (1998) **2**:715; *J. Biol. Chem.* (1999) **274**:9116), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al* (1985) *J. Lab. Clin. Med.* **105**:141-145), and antibodies to VEGF (see, *Nature Biotechnology* (1999) **17**:963-968; Kim *et al* (1993) *Nature **362***:841-844; WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* (2000) **38**:679-692). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* (1998) **80**:10-23), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* (2001) **101**:329-354). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U,S, Ser. No. 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR (for example those disclosed in WO 03/059951), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

"Apoptosis inducing agents" include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1*H*-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-*N*-methyl-4,2-pyrrolocarbonylimino[*N*-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$,$\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\beta_5\alpha_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include *N*-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1*H*-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7*H*-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-

bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, *N*-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* (1998) **31**:909-913; *J. Biol. Chem.* (1999) **274**:9116-9121; *Invest. Ophthalmol Vis. Sci.* (2000) **41**:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* (2001) **119**:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(*R*)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with anti-viral agents (such as nucleoside analogs including ganciclovir for the treatment of cancer. See WO 98/04290.

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall *et al, Am J Hum Genet* (1997) **61**:785-789 and Kufe *et al, Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000. Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August (1998) **5(8)**:1105-13), and interferon gamma (*J Immunol* (2000) **164**:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention

or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, $GABA_B$ receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1*H*,4*H*-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous cythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interfers with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interfers with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

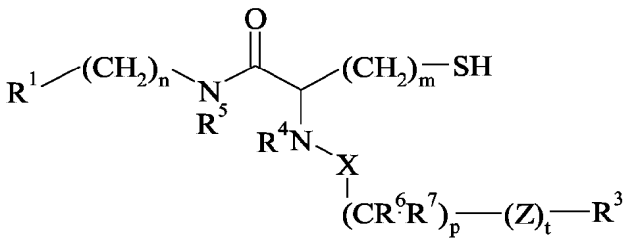
And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

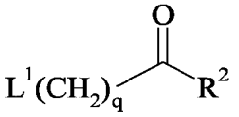
The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of cell proliferation and survival signaling, an agent that interfers with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

These and other aspects of the invention will be apparent from the teachings contained herein.

Compounds of formula I wherein Y is S may be prepared by reacting a compound of formula II with a compound of formula III:



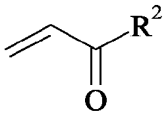
(II)



(III)

wherein m, n, p, q, t, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Z are as defined above and L^1 is a leaving group such as a halogen, for example iodine, chlorine or bromine. The reaction is generally carried out in the presence of a base such as potassium carbonate and in a solvent such as DMF at about room temperature.

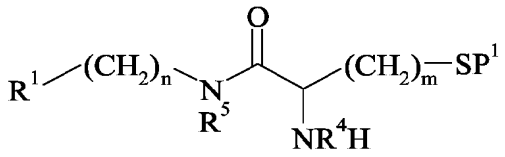
Compounds of formula I wherein Y is S and q is 2 may alternatively be prepared by reacting a compound of formula II with a compound of formula IV:



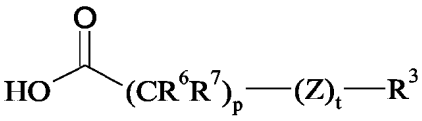
(IV)

wherein R^2 is as defined above. The reaction is generally carried out in the presence of a base such as potassium carbonate and in a solvent such as DMF at about room temperature.

Compounds of formula II wherein X is CO can be prepared by reacting a compound of formula V with a compound of formula VI:



(V)

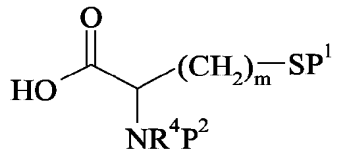


(VI)

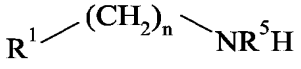
wherein m, n, p, t, R^1, R^3, R^4, R^5, R^6, R^7 and Z are as defined above and P^1 is a suitable protecting group such as trityl. The reaction is generally carried out in the presence of coupling agents such as EDCl and HOBt, a base such as Et_3N and in a solvent such as DMF at about room temperature. Removal of the

protecting group can subsequently be accomplished by using suitable deprotecting agents such as tri-iso-propylsilane and 1,2-ethanedithiol, in solvents such as TFA and water at about room temperature.

Compounds of formula V can be prepared by reacting a compound of formula VII with a compound of formula VIII:



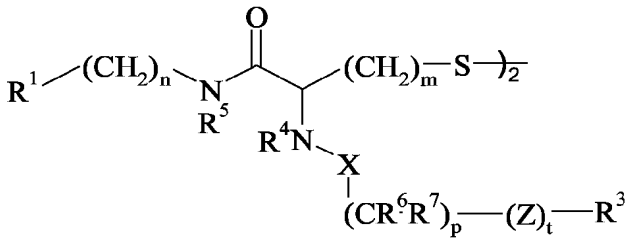
(VII)



(VIII)

wherein m, n, R^1, R^4, R^5 and P^1 are as defined above and P^2 is a suitable protecting group such as Fmoc. The reaction is generally carried out in the presence of coupling agents such as EDCl and HOBt, a base such as Et_3N and in a solvent such as DMF at about room temperature. Removal of the protecting group can subsequently be accomplished by using a suitable deprotecting agent such as piperidine, in a solvent such as DMF at about room temperature.

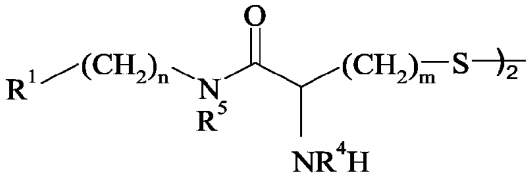
Compounds of formula II can alternatively be prepared from a protected compound of formula IX:



(IX)

wherein m, n, p, t, R^1, R^3, R^4, R^5, R^6, R^7, X and Z are as defined above. The disulfide bond can readily be cleaved using an agent such as tributyl phosphine, in solvents such as THF, methanol and water at about room temperature.

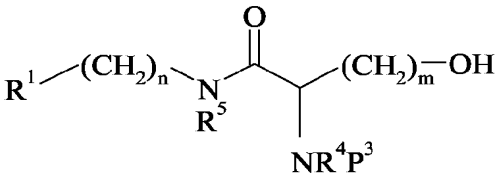
Compounds of formula IX wherein X is CO can be prepared by reacting a compound of formula VI with a compound of formula X:



(X)

wherein m, n, R^1, R^4 and R^5 are as defined above, generally in the presence of coupling agents such as EDCl and HOBt, in a base such as Et_3N and in a solvent such as DMF at about room temperature.

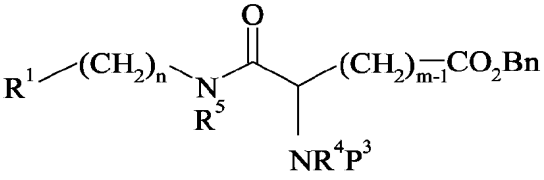
Compounds of formula X can be prepared by reacting a compound of formula XI:



(XI)

wherein m, n, R^1, R^4 and R^5 are as defined above and P^3 is a protecting group such as Boc with methanesulfonyl chloride, generally in the presence of a base such as Et_3N, in a solvent such as DCM at about 0°C, followed by displacement with potassium thioacetate in a solvent such as DMF and removal of the acetate group with an appropriate reagent such as potassium carbonate, in a solvent such as methanol at about room temperature. Removal of the protecting group can subsequently be accomplished by using suitable deprotecting agents such as TFA and DCM at about room temperature.

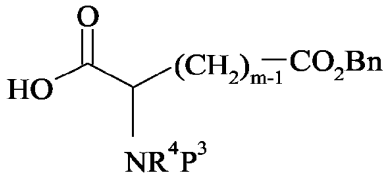
Compounds of formula XI can be prepared by reacting a compound of formula XII:



(XII)

wherein m, n, R^1, R^4, R^5 and P^3 are as defined above, with a reducing agent such as $NaBH_4$, generally in solvents such as THF and MeOH at a temperature of about 50°C.

Compounds of formula XII can be prepared by reacting a compound of formula VIII with a compound of formula XIII:

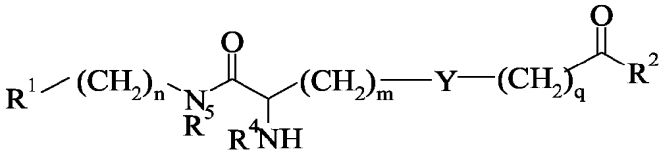


(XIII)

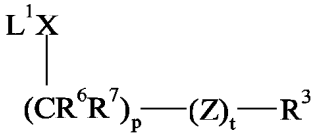
wherein m, R^4 and P^3 are as defined above. The reaction is generally carried out in the presence of a coupling agent such as PyBroP (Bromo-tris-pyrrolidino phosphoniumhexafluorophosphate), a base such as Et_3N and in a solvent as DCM at about room temperature.

Compounds of formula I wherein Y is SO can be prepared by reacting a compound of formula II with an oxidising agent such as OsO_4 (osmium tetraoxide), generally in solvents such as THF and ^tBuOH at about room temperature. Further oxidation of such compounds under similar reaction conditions yields compounds of formula I wherein Y is SO_2.

Compounds of formula I can alternatively be prepared by reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

wherein m, n, p, q, t, R^1 R^2, R^3, R^4, R^5, R^6, R^7, X, Y, Z and L^1 are as defined above. The reaction is generally carried out in the presence of a base such as Et_3N and in a solvent such as DCM at about room temperature.

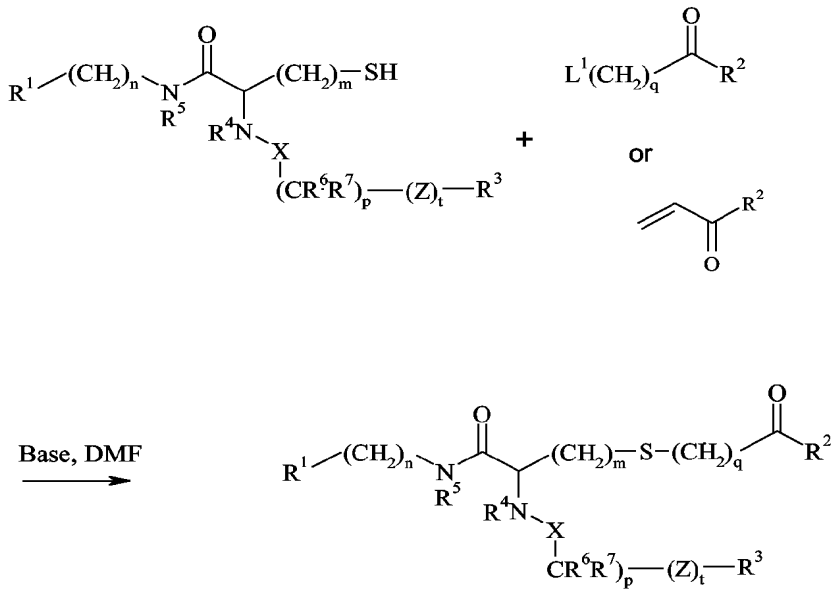
Compounds of formula XIV and XV can be prepared by extension of the processes described above.

Where the synthesis of intermediates and starting materials is not described, these compounds are commercially available or can be made from commercially available compounds by standard methods or by extension of the Examples herein.

Compounds of formula I may be converted to other compounds of formula I by known methods or by methods described in the Examples.

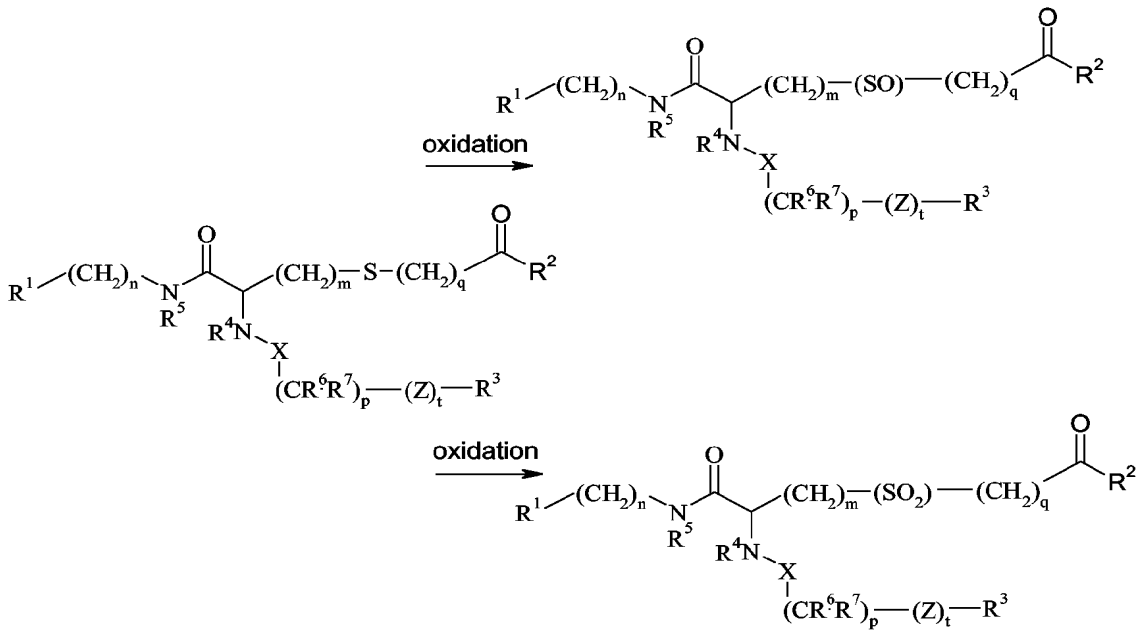
During any of the synthetic sequences described herein it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protecting Groups in Organic Synthesis*, 3rd Edition, Greene, T. W. and Wuts, P. G. M.; Wiley Interscience, 1999 and Kocienski, P. J. *Protecting Groups*, Thieme, 1994. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Compounds of this invention can be prepared as described in **Scheme 1** by taking a functionalised α-amino acid derivative, for instance, cysteine, homocysteine or homologs and performing an alkylation reaction with the appropriate alkyl halide, or a suitable alternative alkylating agent such as an α,β-unsaturated carbonyl compound.



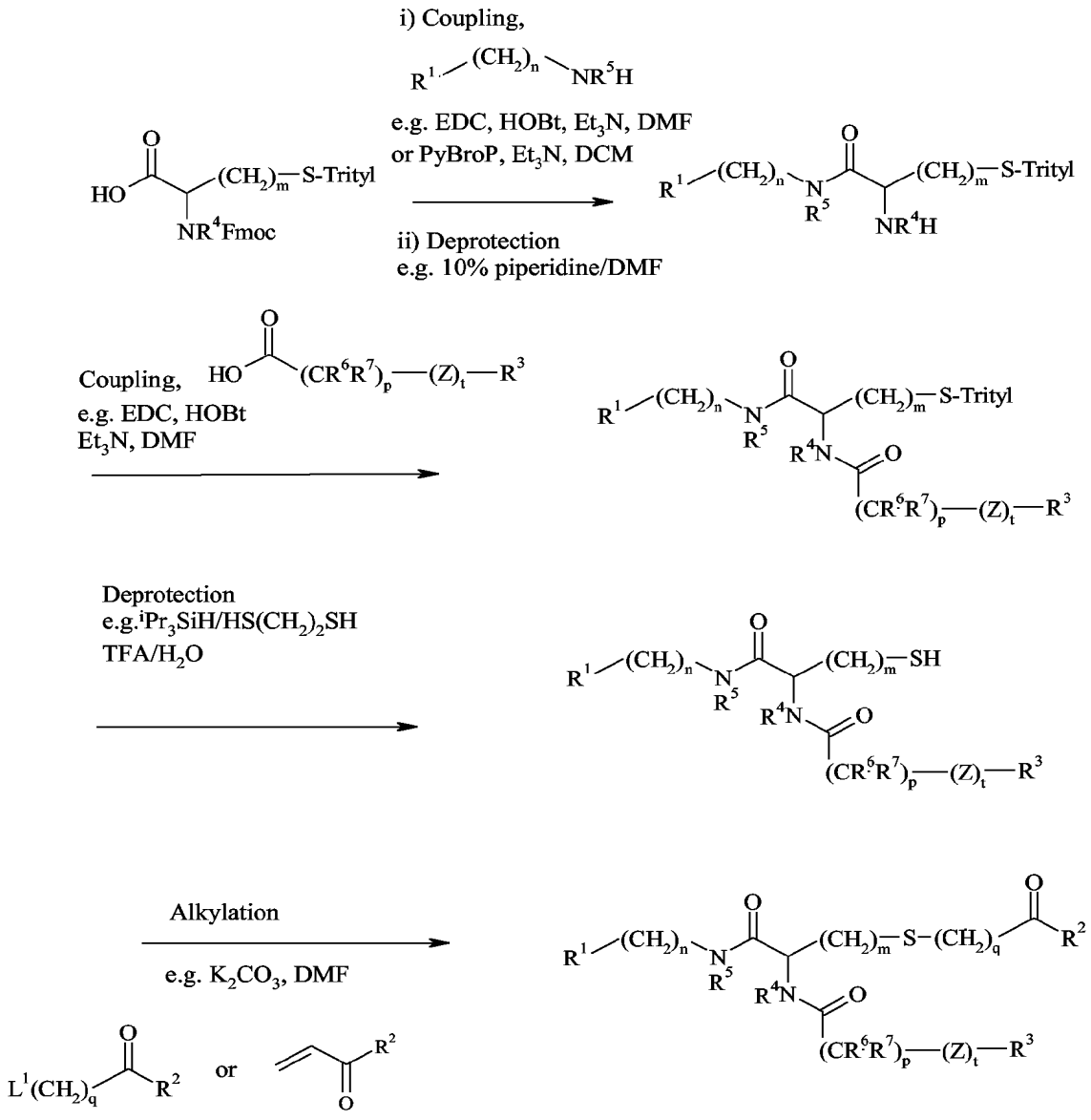
Scheme 1

After the formation of the sulfide, these can readily be oxidized to the corresponding sulfoxide or sulfone using one or two equivalents of a suitable oxidizing agent such as osmium tetraoxide, as shown in **Scheme 2**.



Scheme 2

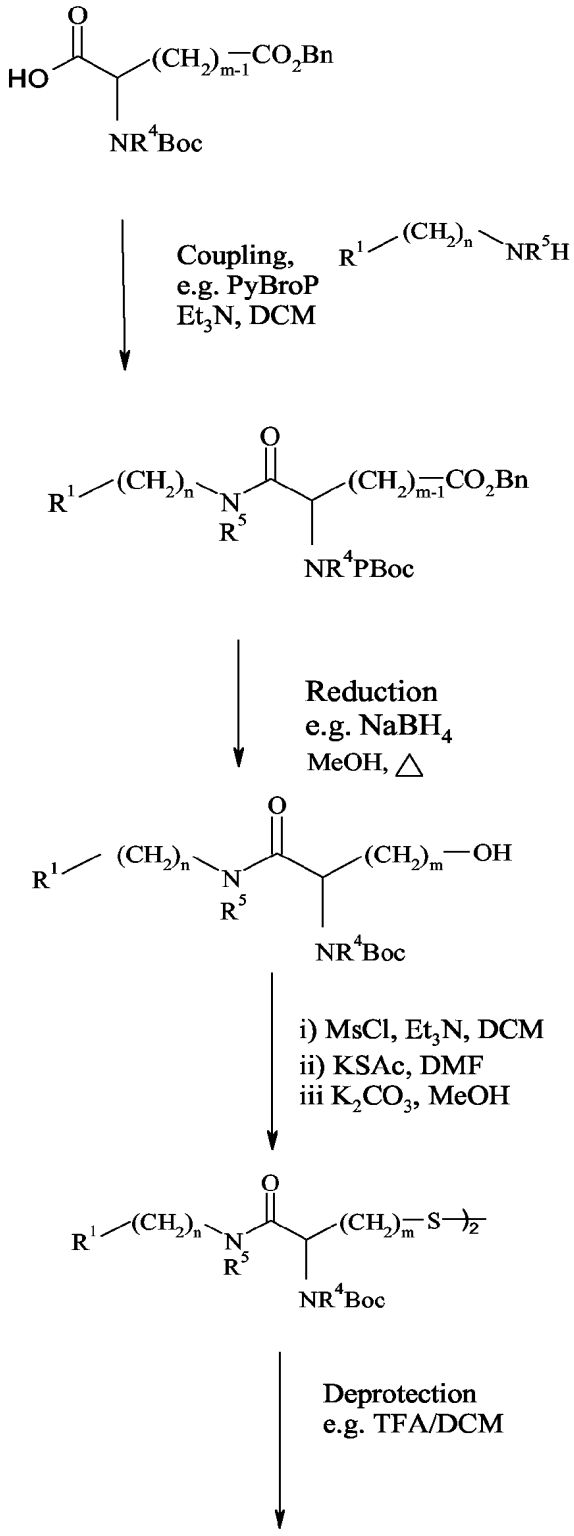
Suitably elaborated precursors are available from commercially available fragments. For instances, starting from Fmoc-*S*-trityl-*L*-cysteine or Fmoc-*S*-trityl-*L*-homocysteine and coupling with an amine yields the corresponding amide, removal of the Fmoc group, e.g. using piperidine in DMF, yields the amine which can be elaborated to yield the *bis*-amide after a second coupling. Cleavage of the trityl protecting group can be accomplished with tri-*iso*-propylsilane and 1,2-ethanedithiol in TFA and H_2O as described in *Tetrahedron Lett.* (1989) **30**:2739 and finally alkylation in the presence of a base such as K_2CO_3 yields the desired inhibitors (**Scheme 3**). These can be oxidized with reagents such as osmium tetraoxide to yield inhibitors in a higher oxidation state, as described in Scheme 2.

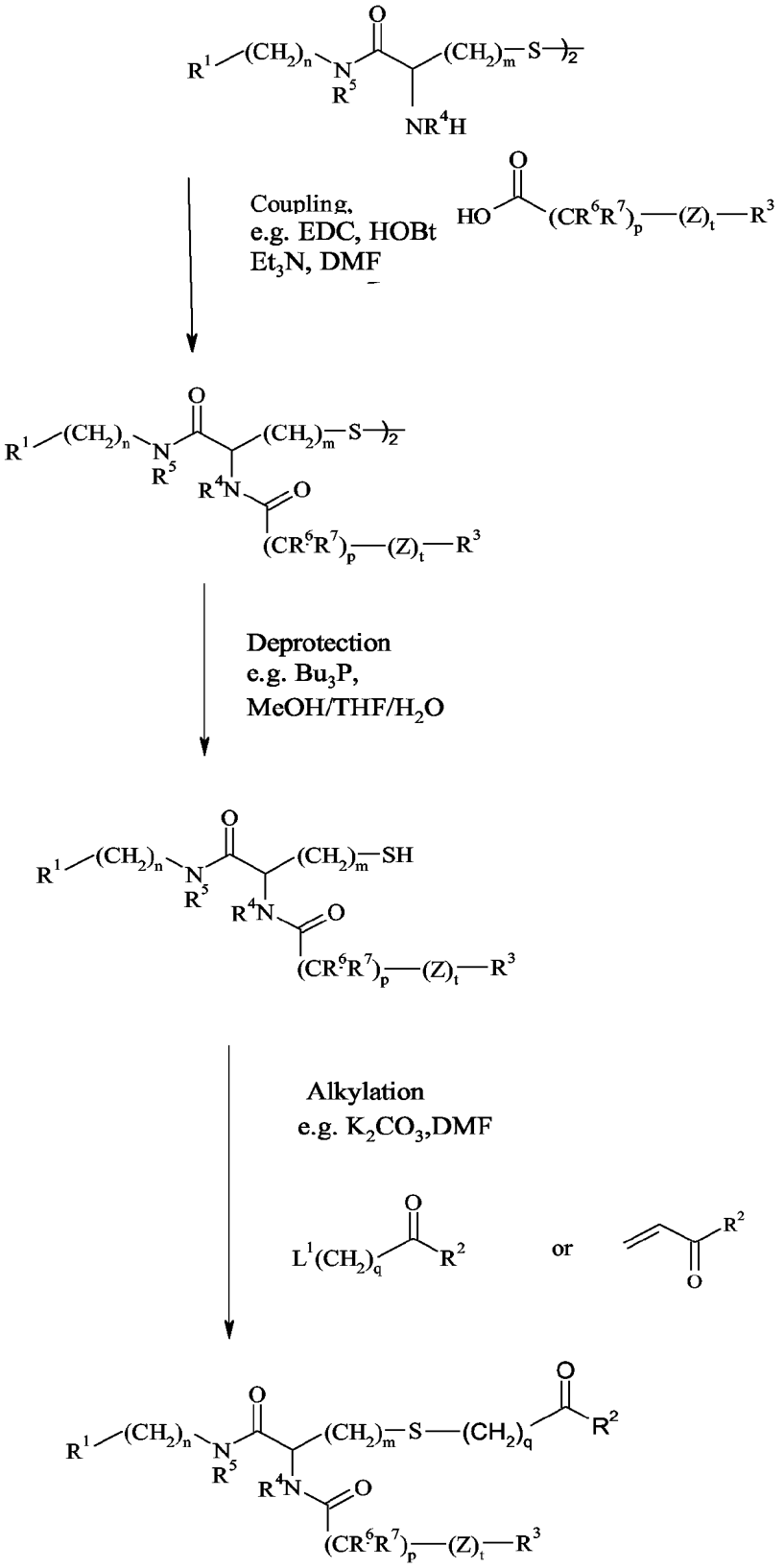


Scheme 3

When suitably elaborated precursors are not commercially available they can be prepared readily, for instance, the isomeric sulfides and derivatives can be synthesised from Boc-*L*-glutamic acid 5-benzyl ester. Coupling of this material gives the requisite amide, which can then be reduced as described in *Bioorg. Med. Chem.* (2002) **10**:2445 using $NaBH_4$ in refluxing methanol. Conversion to the mesylate using methanesulfonyl chloride in the presence of Et_3N at 0°C followed by displacement with potassium thioacetate introduces the sulfur atom. Removal of the acetate group can be achieved with potassium carbonate in methanol, resulting in simultaneous dimerisation. Protecting group removal using trifluoroacetic acid followed by amide coupling allows the second amide to be performed. Reduction of the disulfide bond with tributylphosphine as described by *J. Org. Chem.* (2003) **68**:5641 and *Tetrahedron*

Lett. (1986) **27**:4623 liberates the free thiol, which can be alkylated to give the required inhibitors which can be oxidized as described above (**Scheme 4**).




Coupling,
e.g. EDC, HOBt
Et3N, DMF
Deprotection
e.g. Bu3P,
MeOH/THF/H2O
Alkylation
e.g. K2CO3,DMF
or

Scheme 4

The exemplified compounds described herein were tested by the assays described below and were found to have an IC_{50} value of less than 10μM in one or more of the assays.

HDAC1 and NE Assays

Assay Description:

The HDAC_NE and HDAC1 assays are used to quantify the histone deacetylase (HDAC) activity. The assay is performed in 96 well microtiter plates by pre-incubating serial dilutions of compounds with a fixed concentration of HeLa nuclear extract or purified HDAC1 and then adding an acetylated lysine-containing substrate/developer that fluoresces upon deacetylation. The deacetylase reaction is performed at 37 °C for 60min, terminated by addition of the developer solution, and then fluorescence (ex 360nM, em 460nM) is measured using a plate reader.

HDAC Substrate Buffer System

Reagents of the HDAC Fluorescent Activity Assay are purchased from BioMol Research Laboratories (Plymouth Meeting, PA) and feature the Fluor-de-Lys™ Substrate/Developer System. The reagents include the proprietary fluorescent substrate as a 50mM stock solution (KI-104), and the Developer Concentrate (KI-105). Deacetylation of the lysine residue of the Fluor-de-Lys substrate is quantified by measuring the fluorescence (ex 360nM, em 460nM) after addition of the proprietary Developer.

Working Reagents:

TSA Stock: TSA is provided as a 10mM stock solution in 100% dimethylsulfoxide (DMSO).

Assay Buffer: 25mM Tris/HCl pH8, 137mM NaCl, 2.7mM KCl, 1mM MgCl2, 0.1mg/ml BSA

Diluted Substrate Solution: The commercial 50mM Fluor-de-Lys substrate (KI-104) is diluted to 150uM with HDAC Assay Buffer prior to each use. The final concentration in the assay is 30uM.

Diluted Developer Solution: The commercial 20X Developer Concentrate (KI-105) is diluted 1:167 into HDAC Assay Buffer. 2uM [final] TSA to this solution increases its ability to stop the reaction.

HDAC_NE Working Solution: The HeLa nuclear extract is diluted in assay buffer prior to each use from a fresh aliquot. The final concentration in the assay is 20ug/ml.

HDAC1 Working Solution: The HDAC1 enzyme is diluted in assay buffer prior to each use from a fresh aliquot of enzyme. The final concentration in the assay is 1-2 nM.

Compounds: Test compounds should be prepared as a 10x 5% DMSO solution in assay buffer. The final DMSO concentration in the reaction is 0.5%.

Experimental Design:

The reaction is performed in 96-well microplate in a final volume of 50ul/well, as following:

- Add 5ul of DMSO/compound solution
- Add 35ul of HeLa NE or HDAC1 in assay buffer (or 35ul assay buffer in the negative controls)
- Incubate 10' at room temperature
- Start the reaction by adding 10ul of the 150uM Substrate Solution
- Incubate 1h at 37°C

- Stop by adding 50ul of Developer/4uM TSA solution
- Incubate 10 min at room temperature
- Measure the fluorescence at Ex.360nM and Em.460nM

Protocol for nuclei extraction from HeLa cells (adherent or in suspension)

For a protocol on Nuclei extraction from HeLa S3 cells (adherent or in suspension) refer to Nare et al. 1999 *Anal. Biochem.,* 267: 390-396.

Nuclei preparation for adherent HeLa S3 cells (0.5-1 x 109 cells) is as follows: wash cells twice with 1x PBS, scrape cells into 1X PBS, wash plates with 1X PBS, pool and spin cells at 800 x g 10 minutes at 4°C, wash cell pellets with 1X PBS (count cells), spin cells at 800 x g 10 minutes at 4°C, freeze cell pellets in liquid nitrogen and store -80°C.

Nuclei preparation for HeLa S3 cells in suspension (0.5-1 x 109 cells) is as follows: collect cells by centrifugation at 800 x g 10 minutes at 4°C, wash cell pellets with 1X PBS, spin cells at 800 x g 10 minutes at 4°C, repeat wash step twice (count cells), freeze cell pellet in liquid nitrogen and store at -80°C.

Resuspend cell pellets in lysis buffer (5 ml / 1 x 108 cells; buffer contains: 0.25M sucrose, 0.45% NP40, 10mM Tris-HCl (7.5), 10mM NaCl, 5mM $MgCl_2$, 0.1mM EGTA, 0.5mM PMSF, COMPLETE protease inhibitor mix), vortex 10 sec and leave on ice for 15 minutes, spin through cushion (25 ml of lysate / 5 ml cushion; cushion contains: 30% sucrose, 10mM Tris-HCl (7.5), 10mM NaCl, 3mM $MgCl_2$), spin through cushion at 1,300 x g 10 minutes at 4°C, remove super / cushion, resuspend in lysis buffer as above and re-spin through cushion as above, remove super / cushion.

For nuclear extraction, resuspend nuclear pellets in nuclei extraction buffer (13.5 ml / 5 ml nuclear pellet; nuclei extraction buffer contains: 50 mM Hepes pH 7.4, sonicate into suspension on ice (1 min, output control between 4 and 5), leave on ice 30 min., centrifuge 100,000 x g for 1 hr at 4°C, keep super on ice, repeat sonication/ice/centrifuge steps two more times, pool three supernatants and dialyze in 50 mM Hepes pH 7.4 / 10% glycerol and Snap-freeze suitable aliquots in liquid nitrogen and store -80°C.

Extraction and purification protocol for flag-tagged HDACl expressed in HeLa cells

HeLa cells transiently transfected with pCDNA3-HDAC1-FLAG are grown to 80% confluence on 10 cm culture dishes in DMEM, 10% Fetal bovine serum supplemented with antibiotics and glutamine. Cells are washed with 10 ml cold PBS and scraped into 2 ml of PBS. Cells are centrifuged for 5 minutes at 800 x g at 4°C, washed with 30 ml PBS and resuspended in 10 ml PBS, counted, re-centrifuged and frozen at -80°C.

The frozen cell pellet is re-suspended in 1 ml of hypotonic lysis buffer (LB: 20 mM Hepes pH7.9, 0.25 mM EDTA, 10% glycerol) containing COMPLETE protease inhibitor and incubated on ice for 15 minutes, followed by homogenization on a 2-ml DounceB homogenizer (25 strokes). 150 mM KCl and 0.5% NP-40 are added to the homogenate and the solution is sonicated twice for 30 seconds (output5/6, duty cycle 90) and incubated for 1 hour at 4°C. After a 30 minutes centrifugation at 12000rpm and 4°C the supernatant (soluble extract) is collected and protein concentration is determined using the BIORAD assay.

Anti-FLAG M2 affinity resin (Sigma) is washed three times with TBS and twice with LB. 10 µl of the LB-washed resin/mg of protein (2-3 ug of Flagged-HDAC1) are added to the soluble extract (1 mL) and incubated overnight at 4°C with gentle mixing. The resin is then collected by centrifugation, washed once with LB, twice with LB + 0.1% NP40 and twice with elution buffer (50 mM Hepes pH 7.4, 5% glycerol, 100 mM KCl, 0.01% Triton X-100).

The affinity-purified HDAC is eluted from the resin by addition of a 10-fold excess (with respect to the resin) of elution buffer containing 100 µg/ml 3XFLAG peptide (SIGMA). The concentration of purified HDAC is determined by Western blot analysis.

HDACs 4 and 6 assays

HDAC 4 expression and affinity purification

The His-tagged HDAC 4, wild-type catalytic domain, was expressed in *E. coli* strain BL21 Star™ (DE3). The cells were grown at 37°C in minimum medium supplemented with 1 g/l $(^{15}NH_4)_2SO_4$ and 5 g/l glucose, and 100µM of $ZnCl_2$ to an optical density of 0.8 at 600nm and induced with IPTG for 16 hr at 23°C. At 23°C more than 80% of the protein was soluble.

Bacterial pellets were resuspended in 25mM Hepes pH 7.5, 200mM KCl, 0.5% NP-40, 20% glycerol 1mM DTT and supplemented with Complete EDTA-free protease inhibitor. Subsequently bacterial pellets were lysed by microfluidizer, and centrifuged at 15000 rpm for 30min.

The soluble fraction was diluted 1:1 with 25mM Hepes pH 7.5, 200 mM KCl, 1 mM DTT and was loaded directly on His Trap HP 5ml (Amersham Biosciences). The protein was eluted at 200mM Imidazole. The fractions with HDAC 4 were diluted 1:3 with 25mM Hepes pH 7.5, 5% glycerol, 0.1% of NP-40, 1 mM DTT. Then the solution was loaded on a Resource Q equilibrated with 25mM Hepes pH 7.5, 10% glycerol, 50mM KCl, 0.1% of NP-40, 1 mM DTT. HDAC 4 was eluted with a salt gradient (0-250)mM of KCl. The product was fractionated by preparative SEC (G-75, Superdex 75 26/60 Amersham Biosciences) (25mM Hepes pH 7.5, 150mM KCl, 0.1% of β-octyl glucopiranoside, 1 mM DTT) to give the final product. Analytical SEC indicated that this product was monomeric. The protein was concentrated at ≈ 100µM.

Flagged-HDAC 6 expression and affinity purification

HEK 293 cells = 6 x10^6cells/10 cm dish were transfected with 15 µg of plasmid DNA using Lipofectamine reagent (Invitrogen) according to the manufacturer's recommendations. After 24 hr, scrape cells in pre-cooled 1x PBS, centrifuge at 1500 x g for 5 min at 4°C, washed twice with 1x PBS, count cells, collect cell pellet by centrifugation and freeze at -80°C.

Resuspend cell pellet in 1 ml of hypotonic lysis buffer (20 mM Hepes pH 7.9, 0.25 mM EDTA, 10% glycerol, 1 mM PMSF, Complete EDTA-free protease inhibitors cocktail from Boehringer) and incubated 15' on ice. Homogenize in Douncer 2 (25 strokes, B pestle), add to the homogenate 150 mM KCl and 0.5 % NP40 (isotonic lysis buffer: ILB). Sonicate twice for 30 sec (output 5/6, duty cycle 90, timer constant), then incubate 60 min on a rotating wheel at 4°C. Centrifuge at 12000 rpm in SS34 rotor for 30 min at 4°C and collect supernatant (soluble extract). Determine total protein concentration (BioRad

reagent) and load 4, 8 and 16 µg of total protein on a 4-12% SDS-PAGE minigel together with 8-16 ng of reference protein. Establish flagged-HDAC6 concentration in the sample by Western blot analysis using an anti-FLAG alkaline phosphatase-conjugated monoclonal antibody (M2-AP, A9469, SIGMA)

Wash the anti-FLAG M2 affiity gel matrix (A2220, SIGMA) 3 times with 1x TBS and twice with ILB, centrifuge each time at 10000 rpm for 30 sec in an Eppendorf microfuge. Incubate slurry at RT for a few minutes before use. Use 10 µl of gel matrix for each 2 µg of flagged-HDAC6 in the soluble extract, mix gel matrix and soluble extract and incubate O/N on a rotating wheel at 4°C. Recover gel matrix by centrifugation and wash it once with ILB, twice with ILB containing 0.1% NP-40, and a further 2 times in elution buffer [50 mM Hepes pH 7.4, 5% glycerol, 0.01% Triton X-100, 100 mM KCl. Elute protein by adding to the gel matrix 10 volumes of elution buffer containing 100 µg/ml of 3x FLAG peptide (F4799, SIGMA) and incubation for 60 min on a rotating wheel at RT; recover eluted protein by centrifugation. Estimate flagged-HDAC6 concentration in the sample by anti-FLAG Western blot analysis (dilute eluted protein 30 folds with SDS-PAGE loading buffer and load 3, 10 and 30 µl, in parallel use 4, 8 and 16 ng of reference protein for quantification). Prepare 50 µl aliquots and snap freeze in liquid N_2 before storage at –80°C

HDAC 4 assay

Working Reagents

TSA Stock: TSA is provided as a 10mM solution in 100% DMSO.

Assay buffer: 25mM Tris/HCl pH8, 137mM NaCl, 2.7mM KCl, 1mM $MgCl_2$, 0.1mg/ml BSA

Diluted substrate solution: *tert*-butyl {(1*S*)-1-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)amino]carbonyl}-5-[(trifluoroacetyl)amino]pentyl}carbamate is diluted to 200µM with Tris 1mM pH 7.4 prior to each use. The final concentration in the assay is 20µM.

Diluted developer solution: The commercial 20X developer concentrate (KI-105, BioMol Research Laboratories) is diluted 1:167 into Tris 1mM pH7.4. 2µM [final] TSA to this solution increases its ability to stop the reaction.

Enzyme working solution: Enzyme is diluted in 1.25x assay buffer prior to each use from a fresh aliquot of enzyme. The final concentration in the assay is 0.2 nM.

Experimental Design:

The reaction is performed in 96-well microplate in a final volume of 50µl/well. Add 5µl of DMSO/compound solution, add 40µl of HDAC 4 enzyme in assay buffer and incubate 10' at RT. Start the reaction by adding 5µl of the 200µM substrate solution and incubate 1 hr at 37°C. Stop the reaction by adding 50µl of developer/4µM TSA solution and incubate 30 min at RT. Measure the fluorescence at ex.360nM and em.460nM.

HDAC 6 assay

Working Reagents:

TSA stock: TSA is provided as a 10mM stock solution in 100% DMSO.

Assay buffer: 20mM Hepes pH 7.5, 137mM NaCl, 2.7mM KCl, 1mM $MgCl_2$, 0.1mg/ml BSA

Diluted substrate solution: The 50mM Fluor-de-Lys™ substrate (KI-104, BioMol Research Laboratories) is diluted to 150μM with HDAC assay buffer prior to each use. The final concentration in the assay is 30μM.

Diluted developer solution: The commercial 20X developer concentrate (KI-105, BioMol Research Laboratories) is diluted 1:167 into HDAC assay buffer. 2μM [final] TSA to this solution increases its ability to stop the reaction.

HDAC 6 working solution: The HDAC 6 enzyme is diluted in assay buffer prior to each use from a fresh aliquot of enzyme. The final concentration in the assay is 1-2 nM.

Experimental Design:

The reaction is performed in 96-well microplate in a final volume of 50μl/well. Add 5μl of DMSO/compound solution and then 35μl of HDAC 6 enzyme in assay buffer (or 35μl assay buffer in the negative controls) and incubate 10' at RT. Start the reaction by adding 10μl of the 150μM substrate solution and incubate for 1 hr at 37°C. Stop the reaction by adding 50μl of developer/4μM TSA solution and incubate 30 min at RT. Measure the fluorescence at ex.360nM and em.460nM.

Abbreviations used in the description of the chemistry and assays and in the Examples below are:

BSA (bovine serum albumin); DCM (dichloromethane); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); DTT (dithiothreitol); EDCI (1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride); EDTA (ethylenediaminetetraacetic acid); em (emission); Et_3N (triethylamine); ex (exitation); Hepes ((N-(2-Hydroxyethyl)piperazine)-N'-(2-ethanesulfonic acid)); HOBt (1-hydroxybenzotriazole); ILB (isotonic lysis buffer); IPTG (Isopropyl-beta-D-thiogalactopyranoside); NP40 (Nonidet P40); PBS (Phosphate buffered saline); O/N overnight; PMSF (phenylmethylsulphonyl fluoride);
RT (room temperature); SEC (size exclusion chromatography); TBS (Tris buffered saline); TFA (trifluoroacetic acid); THF (tetrahydrofuran); Tris-HCl (Tris Hydroxymethylaminoethane); and TSA (Trichostatin A).

Other assays are known in the literature and can be readily performed by those skilled in the art.

The following Examples illustrate the present invention.

Example 1 N^2-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-N^1-2-naphthyl-*S*-(4-oxopentyl)-*L*-cystein amide (A5)

Step 1: N^1-2-Naphthyl-N^2-Fmoc-*S*-trityl-*L*-cysteinamide (A1)

To a stirred solution of Fmoc-S-trityl-L-cysteine (1.0 eq.) in DMF was added Et_3N (1.25 eq.), EDCI (1.1 eq.), HOBt (1.0 eq.) and 2-aminonaphthalene (1.25 eq.) and the resulting reaction mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure while azeotroping with xylene and was then taken up in EtOAc and was washed with 0.5 M HCl solution, then $NaHCO_3$ solution and brine. The organics were then dried (Na_2SO_4) and concentrated under reduced pressure. The

resulting mixture was purified by column chromatography on silica eluting with 30-35% EtOAc/petroleum ether to yield the desired amide (A1). MS(ES) $C_{47}H_{38}N_2O_3S$ requires: 710, found: 733 ($M+Na^+$).

Step 2: *N*^{1}-2-Naphthyl-*S*-trityl-*L*-cysteinamide (A2)

A solution of the above compound (A1) in DMF was treated with piperidine (10% volume) and stirred at RT for 2 hours. The mixture was concentrated under reduced pressure while azeotroping with xylene and the residue was then taken up in EtOAc and was washed with H_2O (2x), and brine. The organics were then dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by column chromatography on silica eluting with 40-100% EtOAc/petroleum ether to yield the desired amine (A2). MS(ES) $C_{32}H_{28}N_2OS$ requires: 488, found: 489 ($M+H^+$).

Step 3: *S*-(Trityl)-N^2-[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-*L*-cysteinamide (A3)

The above amine (A2) was coupled with 5-methoxy-2-methyl-indolyl acetic acid (1.1 eq.) as described in Step 1 and the resulting residue obtained after aqueous work up was used without further purification. ^{1}H NMR (400 MHz, CDCl3) δ 8.56 (1H, broad s), 8.02 (1H, broad s), 7.75-7.62 (5H, m), 7.47-7.15 (18H, m), 6.87 (1H, broad s), 6.81 (1H, dd, J = 8.8, 2.5 Hz), 6.14 (1H, d, J = 7.0 Hz), 4.22 (1H, q, J = 7.8 Hz), 3.68 (3H, s), 3.62 (2H, s), 2.63 (1H, dd, J = 13.0, 5.2 Hz), 2.52 (1H, dd, J = 13.0, 4.0 Hz), 2.28 (3H, s). MS(ES) $C_{44}H_{39}N_3O_3S$ requires: 689, found: 690 ($M+H^+$).

Step 4: *N*^{2}-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-*L*-cysteinamide (A4)

A cleavage cocktail of TFA (20 mL), H_2O (1 mL), 1,2-ethanedithiol (0.5 mL), tri-*iso*-propylsilane (0.4 mL) was prepared and a portion of this mixture was added to the above substrate (A3). The resulting mixture was stirred at RT for 90 min. The suspension there obtained was concentrated under reduced pressure and was then taken up in EtOAc and washed with $NaHCO_3$ solution (3x) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with 50-75% EtOAc/petroleum ether to yield the thiol (A4). ^{1}H NMR (400 MHz, d6-DMSO) δ 10.60 (1H, broad s), 10.35 (1H, broad s), 8.27 (1H, d, J = 7.8 Hz), 8.24 (1H, s), 7.89-7.76 (3H, m), 7.55 (1H, dd, J = 8.8, 2.0 Hz), 7.55 (1H, t, J = 8.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.11 (1H, d, J = 8.8 Hz), 7.06 (1H, s), 6.63 (1H, dd, J = 8.8, 2.5 Hz), 4.61 (1H, q, J = 7.6 Hz), 3.74 (3H, s), 3.57 (1H, d, J = 15.4 Hz), 3.52 (1H, d, J = 15.4 Hz), 2.96-2.76 (2H, m), 2.34 (3H, s), 2.35-2.27 (1H, m). MS(ES) $C_{25}H_{25}N_3O_3S$ requires: 447, found: 448 ($M+H^+$).

Step 5: *N*^{2}-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-*S*-(4-oxopentyl)-*L*-cysteinamide (A5)

To a mixture of the thiol (A4) in DMF was added 5-iodopentan-2-one (1.5 eq.) and K_2CO_3 (2.5 eq.) and the mixture was stirred at RT for 14 hours. The reaction was then neutralized with 6M HCl solution and the desired product was isolated by reverse phase HPLC and the fractions containing the aforementioned compound were freeze dried to yield the desired sulfide (A5). ^{1}H NMR (300 MHz, CDCl3) δ 8.74 (1H, broad s), 8.07 (1H, s), 7.99 (1H, broad s), 7.80-7.71 (3H, m), 7.51-7.35 (3H, m), 7.22 (1H, d, J = 8.6 Hz), 6.94 (1H, d, 2.4 Hz), 6.85-6.75 (2H, m), 4.76 (1H, q, J = 6.4 Hz), 3.78 (3H, s), 3.55-

3.35 (2H, m), 2.96-2.80 (2H, m), 2.50-2.40 (4H, m), 2.40 (3H, s), 2.16 (3H, s), 1.84-1.70 (2H, m). MS(ES) $C_{30}H_{33}N_3O_4S$ requires: 531, found: 532 ($M+H^+$).

Example 2 N^2-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-N^1-2-naphthyl-3-[(4-oxopentyl)sulfinyl]-L-alaninamide (B1)

and

Example 3 N^2-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-N^1-2-naphthyl-3-[(4-oxopentyl)sulfonyl]-L-alaninamide (B2)

To an ice cold solution of Example 1 (A5) in THF was added a solution of osmium tetroxide in ^{t}BuOH (2.5 wt%, 2 eq) and the resulting mixture was stirred at 0°C for 20 min and then at RT for a further 16 hours. The solution was concentrated under reduced pressure and the residue was purified by reverse phase HPLC to yield first the sulfoxide (B1) and secondly the sulfone (B2), the fractions containing the aforementioned compounds were freeze dried to yield the desired products.

Sulfoxide (B1): ^{1}H NMR (400 MHz, d6-DMSO) δ 10.62 (1H, broad s), 10.25 (1H, broad s), 8.48 (1H, d, J = 8.3 Hz), 8.20 (1H, broad s), 7.88-7.78 (3H, m), 7.56 (1H, dd, J = 8.8, 2.0 Hz), 7.47 (1H, td, J = 6.8, 1.1 Hz), 7.42 (1H, td, J = 6.8, 1.1 Hz), 7.11 (1H, d, J = 8.6 Hz), 7.03 (1H, d, J = 2.4 Hz), 6.61 (1H, dd, J = 8.5, 2.4 Hz), 5.02-4.94 (1H, m), 3.70 (3H, s), 3.70-3.40 (4H, m), 3.12-2.98 (2H, m), 2.50-2-43 (2H, m), 2.33 (3H, s), 2.07 (3H, s), 1.78 (2H, app. quintet, J = 7.5 Hz). MS(ES) $C_{30}H_{33}N_3O_5S$ requires: 547, found: 548 ($M+H^+$).

Sulfone (B2): ^{1}H NMR (400 MHz, d6-DMSO) δ 10.63 (1H, broad s), 10.35 (0.5 H, broad s), 10.28 (0.5 H, broad s), 8.49 (1H, dd, J = 7.9, 1.6 Hz), 8.24 (1H, d, J = 7.5 Hz), 7.90-7.76 (3H, m), 7.59-7.53 (1H, m), 7.51-7.45 (1H, m), 7.44-7.38 (1H, m), 7.11 (1H, d, J = 8.5 Hz), 7.03 (1H, d, J = 2.4 Hz), 6.61 (1H, dd, J = 8.5, 2.4 Hz), 4.90-4.77 (1H, m), 3.80-3.67 (5H, m), 3.37-2.50 (6H, m), 2.32 (3H, s), 2.08 (1.5 H, s), 2.04 (1.5 H, s), 1.92-1.68 (2H, m). MS(ES) $C_{30}H_{33}N_3O_6S$ requires: 563, found: 564 ($M+H^+$).

Example 4 N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-N^1-2-naphthyl-*S*-(3-oxobutyl)-L-homocysteinamide (C2)

Step 1: N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-N^1-2-naphthyl-*L*-homocysteinamide (C1)

This was prepared from Fmoc-*S*-trityl-homocysteine according to Example 1, steps 1 to 4. ^{1}H NMR (400 MHz, d6-DMSO) δ 10.60 (1H, broad s), 10.19 (1H, broad s), 8.28-8.20 (2H, m), 7.87-7.76 (3H, m), 7.56 (1H, dd, J = 8.9, 2.0 Hz), 7.47 (1H, td, J = 6.8, 1.3 Hz), 7.40 (1H, td, J = 7.1, 1.3 Hz), 7.12 (1H, d, J= 8.6 Hz), 7.06 (1H, d, J = 2.3 Hz), 6.60 (1H, dd, J = 8.6, 2.5 Hz), 4.62-4.53 (1H, m), 3.73 (3H, s), 3.55 (1H, d, J = 15.2 Hz), 3.49 (1H, d, J = 15.2 Hz), 2.60-2.28 (3H, m), 2.32 (3H, s), 2.12-1.88 (2H, m). MS(ES) $C_{26}H_{27}N_3O_3S$ requires: 461, found: 462 ($M+H^+$).

Step 2: N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-N^1-2-naphthyl-*S*-(3-oxobutyl)-L-homocysteinamide (C2)

To a mixture of the above thiol (C1) in DMF was added methylvinylketone (1.5 eq.) and K_2CO_3 (2.5 eq.) and the mixture was stirred at RT for 8 hours. The reaction mixture was filtered and the desired

product was isolated by reverse phase HPLC and the fractions containing the aforementioned compound were freeze dried to yield the desired product (C2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, broad s), 8.11 (1H, broad s), 7.98 (1H, broad s), 7.81-7.74 (3H, m), 7.50-7.36 (3H, m), 7.23 (1H, d, J = 8.8 Hz), 6.88 (1H, d, J = 2.4 Hz), 6.83 (1H, dd, 8.5, 2.4 Hz), 6.58 (1H, d, J = 8.1 Hz), 4.87-4.77 (1H, m), 3.76 (3H, s), 3.77-3.72 (2H, m), 2.82-2.61 (4H, m), 2.49 (2H, t, J = 7.0 Hz), 2.41 (3H, s), 2.16 (3H, s), 2.17-2.06 (1H, m), 1.97-1.85 (1H, m). MS(ES) $C_{30}H_{33}N_3O_4S$ requires: 531, found: 532 ($M+H^+$).

Example 5 *N*^{2}-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)thio]-L-norvalinamide (D8)

Step 1: Benzyl *N*^{2}-(*tert*-butoxycarbonyl)-*N*^{1}-2-naphthyl-L-α-glutaminate (D1)

PyBroP (1.1 eq) was added to a stirred mixture of Boc-*L*-glutamic acid 5-benzyl ester (1.0 eq.), 2-aminonaphthalene (1.2 eq) and Et_3N (2.3 eq) in DCM and the mixture was stirred at RT overnight. The reaction was diluted with DCM, and washed with 0.5 N HCl (2 x), $NaHCO_3$ solution and brine and was then dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica eluting with 25-40% EtOAc/petroleum ether to yield the amide (D1). MS(ES) $C_{27}H_{30}N_2O_5$ requires: 462, found: 463 ($M+H^+$).

Step 2: [(1*S*)-4-Hydroxy-1-[(2-naphthalenylamino)carbonyl]butyl]carbamic acid *tert*-butyl ester (D2)

The benzyl ester (D1) was taken up in THF/MeOH (5:1) and then $NaBH_4$ (3 eq.) was added portionwise. The reaction was warmed to 50°C and then heated at that temperature was 5 hours. The reaction was cooled to RT, more $NaBH_4$ (1.5 eq.) was added and then the resulting mixture was heated at 50°C for a further 3 hours. After cooling to RT and the reaction was quenched by the addition of NH_4Cl solution. The organics were extracted with EtOAc (3x) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The desired material was purified by column chromatography on silica eluting with 60-75% EtOAc/petroleum ether to yield the alcohol (D2). ^{1}H NMR (400 MHz, d6-DMSO) δ 10.15 (1H, broad s), 8.28 (1H, broad s), 7.90-7.78 (3H, m), 7.61 (1H, d, J = 8.9 Hz), 7.46 (1H, t, J = 6.8 Hz), 7.39 (1H, t, J = 6.8 Hz), 7.03 (1H, d, J = 7.8 Hz), 4.44 (1H, t, J = 5.1 Hz), 4.12 (1H, q, J = 5.8 Hz), 3.45-3.35 (2H, m), 1.75-1.1 (13H, m). MS(ES) $C_{20}H_{26}N_2O_4$ requires: 358, found: 359 ($M+H^+$).

Step 3: *S*-[(4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-(2-naphthalenylamino)-5-oxopentyl] ethanethioate (D3)

To a stirred suspension of the alcohol (D2) in Et_3N (2 eq.) and DCM at 0°C was added MsCl (1.5 eq) dropwise and the mixture was stirred at 0°C for 1 hour, during which period the starting material dissolved. The mixture was diluted with DCM and was washed with $NaHCO_3$ solution and brine, then dried (Na_2SO_4) and was concentrated under reduced pressure. MS(ES) $C_{21}H_{28}N_2O_6S$ requires: 436, found: 437 ($M+H^+$).

The resulting residue was taken up in DMF and KSAc (3 eq) was added, the mixture was stirred at RT for 2 hours. The solvent was then removed under reduced pressure whilst azeotroping with xylene and the residue obtained was dissolved in EtOAc and H_2O. The layers were separated and the organic

layer was washed with brine, the dried (Na_2SO_4) and concentrated under reduced pressure to yield the thioacetate (D3) which was used without further purification. MS(ES) $C_{22}H_{28}N_2O_4S$ requires: 416, found: 417 ($M+H^+$).

Step 4: (2*S*,2'*R*)-5,5'-Dithio*bis*(2-[(1,1-dimethylethoxy)carbonylamino]-*N*-2-naphthylpentan amide) (D4)

The thioacetate (D3) was taken up in MeOH and K_2CO_3 (1 eq.) was added, the resulting mixture was stirred at RT for 90 min and the reaction was quenched with 1M HCl and the solvent was removed under reduced pressure. A large volume of EtOAc was added, and the mixture was filtered. The organics were separated and washed with brine, dried (Na_2SO_4) and then concentrated under reduced pressure to yield the disulfide (D4). ^1H NMR (400 MHz, d6-DMSO) δ 10.18 (2H, broad s), 8.30 (2H, broad s), 7.93-7.80 (6H, m), 7.61 (2H, d, J = 8.5 Hz), 7.52-7.37 (4H, m), 7.10-7.03 (2H, m), 4.20-4.05 (2H, m), 2.75-2.65 (4H, m), 1.80-1.60 (8H, m), 1.37 (18H, s). MS(ES) $C_{40}H_{50}N_4O_6S_2$ requires: 746, found: 747 ($M+H^+$).

Step 5: (2*S*,2'*R*)-5,5'-Dithiobis(2-amino-*N*-2-naphthylpentanamide) (D5)

The disulfide (D4) was taken up in DCM and treated with TFA (10 % vol.) and the mixture was stirred at RT for 2 hours. The resulting mixture was concentrated under reduced pressure while azeotroping with xylene and was then partitioned between $NaHCO_3$ solution and EtOAc. The mixture was separated and the organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield the desired diamine (D5). MS(ES) $C_{30}H_{34}N_4O_2S_2$ requires: 546, found: 547 ($M+H^+$).

Step 6: (2*S*,2'*R*)-5,5'-Dithio*bis*(2-[(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino]-*N*-2-naphthylpentanamide) (D6)

The bis-amine (D5) was coupled with 5-methoxy-2-methyl-indolyl acetic acid (2.5 eq.) using EDCI (2.5 eq.), HOBt (2.5 eq.) and Et_3N (5 eq.) as described in Example 1, step 1 and the resulting residue was purified by column chromatography on silica eluting with 70% EtOAc/petroleum ether to yield the amide (D6). MS(ES) $C_{54}H_{56}N_6O_6S_2$ requires: 948, found: 950 ($M+2H^+$).

Step 7: 5-Mercapto-N^2-[(5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-N^1-2-naphthyl-L-norvalin amide (D7)

The bis-amide (D6) in THF/MeOH/H_2O (9:9:1) was treated with tributyl phosphine (4 eq.) and the mixture was stirred at RT for 2 hours, then left to stand at RT overnight. The solvent was removed under reduced pressure and the residue was taken up in EtOAc and washed with H_2O and brine. The organics were dried (Na_2SO_4) and concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica eluting with 75% EtOAc/petroleum ether to yield the thiol (D7). ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (1H, broad s), 8.13 (1H, broad s), 8.02 (1H, broad s), 7.75-7.67 (3H, m), 7.48-7.35 (3H, m), 7.19 (1H, d, J = 8.7 Hz), 6.89 (1H, s), 6.82 (1H, dd, J = 8.8, 2.4 Hz), 6.37 (1H, d, J = 8.6 Hz), 4.72 (1H, q, J = 7.9 Hz), 3.74 (3H, s), 3.72 (2H, s), 2.53-2.33 (2H, m), 2.35 (3H, s), 2.05-1.93 (1H, m), 1.74-1.48 (3H, m). MS(ES) $C_{27}H_{29}N_3O_3S$ requires: 475, found: 476 ($M+H^+$).

Step 8: N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-N^1-2-naphthyl-5-[(2-oxopropyl) thio]-L-norvalinamide (D8)

The thiol (D7) was alkylated with chloroacetone (1.5 eq.) as described in Example 1, step 5. After 8 hours, the reaction was quenched by addition of 1 M HCl and the mixture was concentrated under

reduced pressure whilst azeotroping with xylene. The residue was taken up in EtOAc, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with 75% EtOAc/petroleum ether to yield the ketone (D8). ^{1}H NMR (400 MHz, d6-DMSO) δ 10.58 (1H, broad s), 10.20 (1H, broad s), 8.26 (1H, broad s), 8.18 (1H, d, J = 7 Hz), 7.88-7.76 (3H, m), 7.55 (1H, d, J = 8 Hz), 7.46 (1H, t, J = 7 Hz), 7.38 (1H, t, J = 7 Hz), 7.11 (1H, d, J = 8 Hz), 7.04 (1H, broad s), 6.58 (1H, d, J = 7 Hz), 4.50-4.40 (1H, m), 3.73 (3H, s), 3.58-3.40 (2H, m), 2.60-2.40 (4H, m), 2.35 (3H, s), 2.17 (3H, s), 1.90-1.45 (4H, m). MS(ES) $C_{30}H_{33}N_3O_4S$ requires: 531, found: 532 ($M+H^+$).

Example 6 *N*^{2}-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-*L*-norvalinamide (E1)

A solution of the thiol of Example 5, step 7 (D7) in DMF was degassed with a stream of argon and then 3-bromo-1,1,1-trifluoroacetone (1.5 eq.) and K_2CO_3 (1.5 eq.) were added. The mixture was stirred at RT for 90 min under argon, then the reaction was quenched by addition of 1 M HCl. The mixture was purified by reverse phase HPLC and the fractions containing the aforementioned compound were freeze dried to yield the desired product (E1). ^{1}H NMR (400 MHz, d6-DMSO) δ 10.58 (1H, broad s), 10.18 (1H, broad s), 8.24 (1H, broad s), 8.18 (1H, d, J = 8.1 Hz), 7.87-7.77 (3H, m), 7.54 (1H, dd, J = 8.8, 2.0 Hz), 7.46 (1H, t, J = 7 Hz), 7.39 (1H, t, J = 7 Hz), 7.10 (1H, d, J = 8.8 Hz), 7.04 (1H, d, J = 2.2 Hz), 6.59 (1H, dd, J = 8.8, 2.4 Hz), 4.52-4.43 (1H, m), 3.72 (3H, s), 3.55, (1H, d, J = 15.1 Hz), 3.48 (1H, d, J = 15.1 Hz), 2.75 (2H, s), 2.64 (2H, t, J = 7.2 Hz), 2.32 (3H, s), 1.91-1.48 (4H, m). MS(ES) $C_{30}H_{30}F_3N_3O_4S$ requires: 585, found: 586 ($M+H^+$) and 604 ($M+H_2O+H^+$).

Examples 7-13 were made according to the reaction schemes and the processes described in the previous Examples.

Example	Name	M+H$^+$	Procedure of Example
7	(2*S*)-2-{[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]amino}-*N*-2-naphthyl-4-[(3-oxobutyl)sulfonyl]butanamide	564	3
8	*N*^{2}-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)sulfinyl]-*L*-norvalinamide	548	2
9	*N*^{2}-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxopropyl)sulfonyl]-*L*-norvalinamide	564	3
10	*N*^{2}-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(3-Acetoxy-2-oxopropyl)thio]-*L*-norvalinamide	590	5
11	*N*^{2}-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-{[2-oxo-2-(2-thienyl)ethyl]thio}-*L*-norvalinamide	600	5
12	*N*^{2}-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-*N*^{1}-2-naphthyl-5-[(2-oxo-2-phenylethyl)thio]-*L*-norvalinamide	594	5

13	N^2-[(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetyl]-5-{[2-(2-methoxyphenyl)-2-oxoethyl]thio}-N^1-2-naphthyl-*L*-norvalinamide	624	5

Examples 14-22 were made according to the reaction schemes and the processes described in the previous Examples.

Example	Name	MWt	Mass Observed	Procedure of Example
14	N^2-Acetyl-N-(3-acetylphenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	418	419	6
15	N-Benzoylglycyl-N-(3-acetylphenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	537	538	6
16	N-(3-Acetylphenyl)-N^2-(cyanoacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	443	444	6
17	N-(3-Acetylphenyl)-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	496	497	6
18	N-(3-Acetylphenyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	551	552	6
19	tert-Butyl {(1S)-1-[(pyridin-3-ylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate	435	436	6
20	tert-Butyl {(1S)-1-[(2-naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate	484	403 $[M+H_3O^+-100]^+$	6
21	N^2-(tert-Butoxycarbonyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	531	532	6
22	tert-Butyl {(1S)-1-{[(3-acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}carbamate	476	377 $[M+H-100]^+$	6

Example	Name	MWt	Mass Observed	Procedure of Example
23	N-(3-Acetylphenyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	500	501	6
24	N-(3-Acetylphenyl)-N^2-(1H-imidazol-2-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	470	471	6
25	N-Benzoylglycyl-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	560	561	6
26	N^2-(4-Methylpentanoyl)-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	497	498	6
27	N^2-Acetyl-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	441	442	6
28	N-2-Naphthyl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	508	509	6
29	N^2-[(4-Methylpiperazin-1-ium-1-yl)acetyl]-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	502	503	6
30	N^2-(4-Methylpentanoyl)-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	529	530	6
31	N^2-[(1-Methylpiperidinium-4-yl)carbonyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate)	524	525	6
32	N-{(1S)-1-[(2-Naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	489	490	6

Example	Name	MWt	Mass Observed	Procedure of Example
33	N^2-Acetyl-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	473	474	6
34	N-Pyridinium-3-yl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	459	460	6
35	N^2-(1H-Imidazol-3-ium-2-ylcarbonyl)-N-(quinolin-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	493	494	6
36	N^2-[(Methylsulfonyl)acetyl]-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	551	552	6
37	N-Benzoylglycyl-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	592	593	6
38	N^2-Acetyl-N-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	426	427	6
39	N-Benzoylglycyl-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	496	497	6
40	N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	606	607	6
41	N-2-Naphthyl-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	559	560	6
42	N^2-(4-Methylpentanoyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	433	434	6

Example	Name	MWt	Mass Observed	Procedure of Example
43	N^2-[(Methylsulfonyl)acetyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	519	520	6
44	N^2-(Phenylacetyl)-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	549	550	6
45	N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	606	607	6
46	N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	574	575	6
47	N-[(2-Phenyl-1,3-thiazol-4-yl)methyl]-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	525	526	6
48	N^2-(Phenylacetyl)-N-(quinolinium-3-ylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	517	518	6
49	N^2-[(1-Methylpiperidinium-4-yl)carbonyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate)	556	557	6
50	N^2-(Phenylacetyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	453	454	6
51	N-[(2-Phenyl-1,3-thiazol-4-yl)methyl]-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	555	556	6
52	N-2-Naphthyl-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	502	503	6

Example	Name	MWt	Mass Observed	Procedure of Example
53	N-[2-(3-Phenylpyrrolidinium-1-yl)ethyl]-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	536	537	6
54	N-(Quinolinium-3-ylmethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	523	524	6
55	N-[2-(1-Isopropylpiperidinium-4-yl)ethyl]-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	529	530	6
56	N^2-(4-Methylpentanoyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	529	530	6
57	N^2-Acetyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	473	474	6
58	N^2-(Phenylacetyl)-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	549	550	6
59	N^2-[(Dimethylammonio)acetyl]-N-[2-(3-phenylpyrrolidinium-1-yl)ethyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate)	516	517	6
60	N-Benzoylglycyl-N-[(2-phenyl-1,3-thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	592	593	6
61	N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	481	482	6

Example	Name	MWt	Mass Observed	Procedure of Example
62	N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide	532	533	6
63	*N*-{(1*S*)-1-({[2-(1*H*-indol-3-yl)ethyl]amino}carbonyl)-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide	557	558	6
64	N^2-Acetyl-N-(2-hydroxy-2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	420	421	6
65	N^2-Acetyl-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	404	405	6
66	N-{(1S)-1-{[(3-Acetylphenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}-2-(1H-tetrazol-1-yl)benzamide	548	521 $(M+H-N_2)^+$	6
67	N^2-[(Methylsulfonyl)acetyl]-N-2-naphthyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	504	505	6
68	N-{(1S)-1-{[(2-Hydroxy-2-phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	483	484	6
69	N-2-Naphthyl-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	558	559	6
70	N-[2-(1H-Indol-3-yl)ethyl]-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	525	526	6
71	*N*-{(1*S*)-1-{[(2-Phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	467	468	6

Example	Name	MWt	Mass Observed	Procedure of Example
72	N^2-(1H-Imidazol-2-ylcarbonyl)-N-(2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	456	457	6
73	N-{(1S)-1-({[(2-Phenyl-1,3-thiazol-4-yl)methyl]amino}carbonyl)-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide	587	588	6
74	N^2-[(5-Methoxy-2-methyl-1H-indol-3-yl)acetyl]-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	536	537	6
75	2-({(1S)-1-{[(2-Hydroxy-2-phenylethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate	463	464	6
76	N-{(1S)-1-[(2-Naphthylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide	540	541	6
77	N-(Quinolinium-3-ylmethyl)-N^2-[2-(1H-tetrazol-1-yl)benzoyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	571	544 $(M+H-N_2)^+$	6
78	N-(2-Phenylethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	486	487	6
79	N^2-(5-Oxo-5-phenylpentanoyl)-N-[(2-phenyl-1,3-79thiazol-4-yl)methyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	605	606	6
70	N^2-(Cyanoacetyl)-N-pyridinium-3-yl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	402	403	6

Example	Name	MWt	Mass Observed	Procedure of Example
81	N-(2-Hydroxy-2-phenylethyl)-N^2-(1H-imidazol-2-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	472	473	6
82	N-Benzoylglycyl-N-(2-hydroxy-2-phenylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	539	540	6
83	N-(2-Hydroxy-2-phenylethyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	553	554	6
84	N-(2-Hydroxy-2-phenylethyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	496	497	6
85	N-(1-Benzylpiperidinium-4-yl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	606	607	6
86	N-(3,5-Dichlorophenyl)-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	577	577	6
87	N-(1-Benzylpiperidinium-4-yl)-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	551	552	6
88	N-Cyclopentyl-N^2-[(4-methylpiperazin-1-ium-1-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	466	467	6
89	N-(3,5-Dichlorophenyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	521	521	6
90	N-(1-Benzylpiperidinium-4-yl)-N^2-(5-oxo-5-phenylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	605	606	6

Example	Name	MWt	Mass Observed	Procedure of Example
91	N-(1-Benzylpiperidinium-4-yl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	555	556	6
92	2-({(1S)-1-{[(2-Furylmethyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate	423	424	6
93	N-(2-Furylmethyl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	456	457	6
94	N-{(1S)-1-[(Cyclopentylamino)carbonyl]-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	431	432	6
95	N-Benzoylglycyl-N-(1-benzylpiperidinium-4-yl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	592	593	6
96	N^2-[(Methylsulfonyl)acetyl]-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	489	490	6
97	N-(1-Benzylpiperidinium-4-yl)-N^2-(4-methylpentanoyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	529	530	6
98	N^2-Acetyl-N-(3,5-dichlorophenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	444	445	6
99	N-(3,5-Dichlorophenyl)-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	497	497	6
100	N^2-(5-Oxo-5-phenylpentanoyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	543	544	6

Example	Name	MWt	Mass Observed	Procedure of Example
101	N-(3,5-Dichlorophenyl)-N^2-[(1-methylpiperidinium-4-yl)carbonyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	527	528	6
102	N^2-(4-Methylpentanoyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	467	468	6
103	N^2-Acetyl-N-cyclopentyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	368	369	6
104	N-Cyclopentyl-N^2-[(methylsulfonyl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	446	447	6
105	N-{(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}quinoxaline-6-carboxamide	558	559	6
106	N-Cyclopentyl-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	450	451	6
107	N-(1-Benzylpiperidinium-4-yl)-N^2-(phenylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	549	550	6
108	N^2-(Cyanoacetyl)-N-cyclopentyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	393	394	6
109	N-(2-Piperidinium-1-ylethyl)-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	474	475	6
110	N-(2-Piperidinium-1-ylethyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	493	494	6

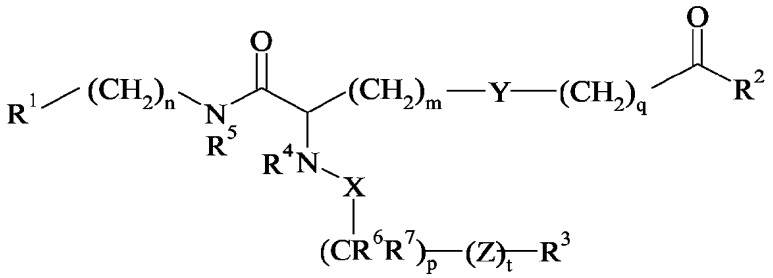
Example	Name	MWt	Mass Observed	Procedure of Example
111	N^2-Acetyl-N-(1-benzylpiperidinium-4-yl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	473	474	6
112	N-Benzoylglycyl-N-(3,5-dichlorophenyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	563	564	6
113	N-(1-Benzylpiperidinium-4-yl)-N^2-(pyridin-3-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	536	537	6
114	N^2-[(2-Oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	544	545	6
115	N-(3,5-Dichlorophenyl)-N^2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)acetyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	577	578	6
116	N-(3,5-Dichlorophenyl)-N^2-(3-thienylacetyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	526	527	6
117	2-({(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}amino)-N,N-dimethyl-2-oxoethanaminium trifluoroacetate	487	488	6
118	N-{(1S)-1-{[(3,5-Dichlorophenyl)amino]carbonyl}-4-[(3,3,3-trifluoro-2-oxopropyl)thio]butyl}nicotinamide	508	509	6
119	N-Benzoylglycyl-N-(2-furylmethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	499	500	6
120	N-(1-Benzylpiperidinium-4-yl)-N^2-[(1-methylpiperidinium-4-yl)carbonyl]-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide bis(trifluoroacetate)	556	557	6

Example	Name	MWt	Mass Observed	Procedure of Example
121	N-Cyclopentyl-N^2-(1H-pyrazol-4-ylcarbonyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide	420	421	6
122	N^2-(Phenylacetyl)-N-(2-piperidinium-1-ylethyl)-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalinamide trifluoroacetate	487	488	6

5

CLAIMS

1. A compound of formula I:



(I)

wherein:

m is 1, 2, 3, 4 or 5;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 1, 2, 3, 4 or 5;

t is 0 or 1;

R^1 is hydrogen, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, $N(R^a)_2$ or a ring which is: C_{3-5}cycloalkyl; C_{6-10}arylC_{1-6}alkyl; C_{6-10}aryloxy; a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring; a 5 or 6 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2, or 3 nitrogen atoms; or a 7-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; said C_{1-6}alkyl or ring being optionally substituted by one or more groups independently chosen from $(CH_2)_vR^b$;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, -(C=O)-$N(R^a)_2$ or a ring which is: C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2, or 3 nitrogen atoms; the ring being optionally substituted by one or more groups independently selected from cyano, halogen, hydroxy, oxo, nitro, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{3-10}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{6-10}aryl;

R^3 is hydrogen; halogen; hydroxy; cyano; C_{1-6}alkyl; haloC_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkoxy; haloC_{1-6}alkoxy; C_{3-10}cycloalkyl; haloC_{3-10}cycloalkyl; C_{2-10}alkenyl; C_{6-10}alkadienyl; C_{2-10}alkynyl; nitro; $N(R^c)_2$ or a ring which is: C_{3-10}cycloalkyl; C_{5-10}cycloalkenyl; C_{6-10}aryl; C_{6-10}arylC_{1-6}alkyl; C_{6-10}aryloxy; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally bridged by a C_{1-4}alkyl group; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; the ring being optionally substituted by one or more groups independently selected from R^d;

R^4, R^6, R^7 and R^8 are independently selected from hydrogen and C_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl; or

R^5, together with N-$(CH_2)_n$-R^1 forms a piperazine ring optionally substituted by up to three substituents selected from $(CH_2)_vR^b$;

each R^a is independently hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

each R^b is independently cyano, halogen, nitro, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylcarbonyl, $SO_2(NR^c)_2$, $N(R^c)_2$, or a ring which is: C_{6-10}aryl, C_{6-10}aryloxy, C_{6-10}arylcarbonyl, a 5 or 6 membered saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; any of which rings being optionally substituted by one or more groups independently selected from cyano, halogen, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy and haloC_{1-6}alkoxy;

each R^c is independently hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, carboxy or a ring which is: C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl or C_{6-10}arylcarbonyl, the ring being optionally substituted by one or more groups independently selected from amino, hydroxy, nitro, cyano, halogen and C_{1-6}alkyl;

each R^d is independently halogen, hydroxy, oxo, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carboxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, $SO_2N(R^c)_2$, $N(R^c)_2$, SO_2R^e, $(CH_2)_w(CO)N(R^f)_2$, $O(CH_2)_yN(R^f)_2$ or a ring which is: C_{6-10}aryl; C_{6-10}arylC_{1-6}alkyl, 5 or 6 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O or S, optionally bridged by a C_{1-4}alkyl group; 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; the ring being optionally substituted by one or more groups independently selected from halogen, hydroxy, amino, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy and haloC_{1-6}alkoxy;

R^e is C_{1-6}alkyl or C_{6-10}aryl;

each R^f is independently hydrogen, C_{1-8}alkyl, aminoC_{1-8}alkyl, C_{1-6}alkylaminoC_{1-8}alkyl, di(C_{1-6}alkyl)aminoC_{1-8}alkyl, C_{1-6}alkyloxycarbonyl, C_{6-10}aryloxycarbonyl, C_{6-10}aryloxycarbonylaminoC_{1-8}alkyl or C_{6-10}arylC_{1-6}alkyloxycarbonylaminoC_{1-8}alkyl;

X is CH_2, C=O, C=O(O), (C=O)(NR^8), (C=S)(NR^8) or SO_2;

Y is S, SO or SO_2;

Z is (CH=CH), C=O, SO_2 or S;

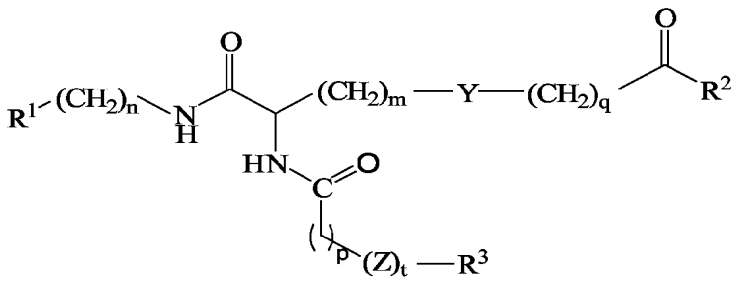
v is 0, 1, 2, or 3;

w is 0, 1, 2 or 3; and

y is 1, 2, 3, 4, 5, 6, 7 or 8;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. A compound according to claim 1 of formula IA:



(IA)

wherein:

m is 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 1, 2 or 3;

t is 0 or 1;

R^1 is C_{1-4}alkyl, C_{1-4}alkoxy, $N(R^a)_2$ wherein R^a is independently selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkylcarbonyl or a ring which is: C_{3-10}cycloalkyl, phenoxy, phenyl, naphthyl, a 9-13 membered partially saturated hydrocarbon ring, a 5 or 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms or a 9-10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S; said alkyl or ring being optionally substituted by one, two or three groups independently chosen from $(CH_2)_vR^b$;

R^2 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl; or a ring which is C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl or a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S, the ring being optionally substituted by one, two or three groups independently selected from cyano, halogen, hydroxy, oxo or C_{1-6}alkoxy;

R^3 is hydrogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, $N(R^c)_2$, C_{6-10}alkadienyl or a ring which is: C_{3-7}cycloalkyl; C_{5-8}cycloalkenyl; phenyl; benzyl; phenoxy; naphthyl; a 4, 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally bridged by a C_{1-2}alkyl group; a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, but not more than one of which is O or S; a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; or a 7, 8, 9 or 10 membered saturated, partially saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; the ring being optionally substituted by one, two or three groups independently selected from R^d;

v is 0 or 1;

each R^b is independently cyano, halogen, oxo, hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, $SO_2N(R^c)_2$, $N(R^c)_2$ or a ring which is: C_{6-10}aryl, C_{6-10}arylcarbonyl, a 6 membered saturated heterocycle containing 1 or 2 heteroatoms independently selected from N and O, a 5 membered unsaturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, or a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms; any of which rings being optionally substituted by one, two or three groups independently selected from halogen and C_{1-6}alkoxy;

each R^c is independently hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}arylC_{1-6}alkyl or C_{6-10}arylcarbonyl;

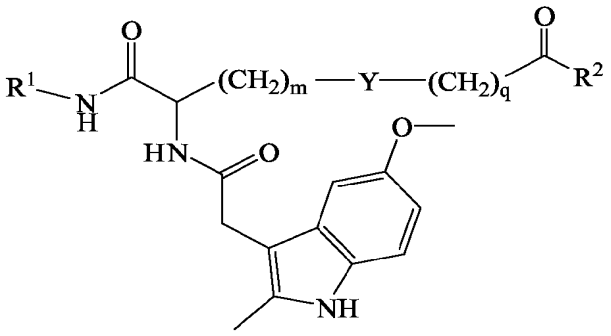
each R^d is independently bromine, chlorine, fluorine, oxo, cyano, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, acetyl, trifluoroacetyl, methoxy, diethylamino, acetylamino, methylsulfonyl, phenylsulfonyl, [(aminohexyl)amino](oxo)ethyl, [(benzyloxycarbonylamino)hexylamino](oxo)ethyl, (butyloxycarbonylamino)hexoxy; or a phenyl, benzyl, tetrazolyl or pyrrolyl ring, the ring being optionally substituted by one, two or three groups independently selected from bromine, chlorine, fluorine, methyl and methoxy;

Y is S, SO or SO_2; and

Z is C=O or SO_2;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. A compound according to claim 1 or 2 of formula IB:



(IB)

wherein m, q, R^1, R^2 and Y are as defined in claim 1 or 2;
or a pharmaceutically acceptable salt or stereoisomer thereof.

4. A compound according to any previous claim wherein:

R^1 is methyl, methoxy, $N(R^a)_2$ wherein R^a is independently selected from hydrogen, methyl and acetyl or a ring which is: indolyl, phenyl, isoquinolinyl, imidazopyridinyl, pyrrolidinyl, benzoimidazolyl, cyclopentyl, pyridazinyl, piperidinyl, morpholinyl, furyl, imidazolyl, phenoxy, quinolinyl, thiazolyl, tetrahydronaphthalenyl, dihydroindolyl, pyridinyl, naphthyl, tetrahydrobenzo[7]annulenyl, dihydroindenyl, dihydroisochromenyl, cyclohexyl, benzothiazolyl, isoxazolyl, piperazinyl, cycloheptyl, octahydroquinolizinyl, tetrahydroquinolinyl, benzoxazolyl and thienyl; said methyl or ring being optionally substituted by up to three substituents selected from $(CH_2)_vR^b$;

v is 0 or 1; and

R^b is cyano, chlorine, fluorine, oxo, hydroxy, methyl, ethyl, isopropyl, methoxy, ethoxy, aminosulfonyl, acetyl, trifluoromethyl, acetylamino or a ring which is: phenyl, triazolyl, imidazolyl, morpholinyl, pyrimidinyl, pyridinyl, benzoyl, piperidinyl or pyrrolyl; any of which rings being optionally substituted by one or more groups independently selected from chlorine and methoxy.

5. A compound according to any one of claims 1, 2, and 4 wherein:

R^3 is hydrogen, cyano, C_{1-4}alkyl, haloC_{1-4}alkyl, $N(R^c)_2$, C_{6-10}alkadienyl or a ring which is: indolyl, benzofuranyl, chromenyl, tetrahydroisoquinolinyl, pyridinyl, naphthyl, benzodioxolyl, thienyl, thiadiazolyl, cyclopropyl, cyclohexyl, thiazolidinyl, phenyl, isoquinolinyl, cyclopentyl, bicycloheptyl, pyrazinyl, piperidinyl, napthyridinyl, quinoxalinyl, quinolinyl, pyrazolyl, dihydroisoindolyl, triazolyl, hydrobenzoxazolyl, thiazolyl, dihydrotriazolyl, dihydrobenzodioxinyl, imidazolyl, azepanyl, isoxazolyl, cyclopentenyl, pyrrolyl, cyclohexenyl, furyl, cycloheptyl, benzimidazolyl, dihydrobenzofuryl, phenoxy, tetrahydropyranyl, morpholinyl, piperazinyl, triazolopyrimidinyl, pyrrolidinyl, dihydroimidazolyl, oxazolidinyl, benzimidazolyl, azetidinyl, azabicycloheptyl, octahydroisoindolyl, benzothiadiazolyl, dihydrobenzoxazinyl, benzothienyl or dihydrobenzoxazolyl; the ring being optionally substituted by one or more groups independently selected from R^d;

each R^c is independently hydrogen, methyl, ethyl, acetyl, benzyl or benzoyl; and

R^d is bromine, chlorine, fluorine, oxo, cyano, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, acetyl, trifluoroacetyl, methoxy, diethylamino, acetylamino, methylsulfonyl, phenylsulfonyl, [(aminohexyl)amino](oxo)ethyl, [(benzyloxycarbonylamino)hexylamino](oxo)ethyl, (butyloxycarbonylamino)hexoxy; or a phenyl, benzyl, tetrazolyl or pyrrolyl ring, the ring being optionally substituted by one or more groups independently selected from bromine, chlorine, fluorine, methyl and methoxy.

6. A pharmaceutical composition comprising a compound of any preceding claim or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

7. A compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof for use in therapy.

8. The use of a compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a disease ameliorated by modulating HDAC activity.

9. The use of a compound according to any one of claims 1-5, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a disease selected from cancer, neurodegenerative diseases, schizophrenia, stroke, restenosis and mental retardation.

10. A method of treating or preventing a disease selected from cancer, neurodegenerative diseases, schizophrenia, stroke, restenosis and mental redardation in a subject, which comprises administration to that subject an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.